Supplementary Information

Synthesis of isolable β-chloroenamines from *N*-alkoxylactams with organometallic reagents

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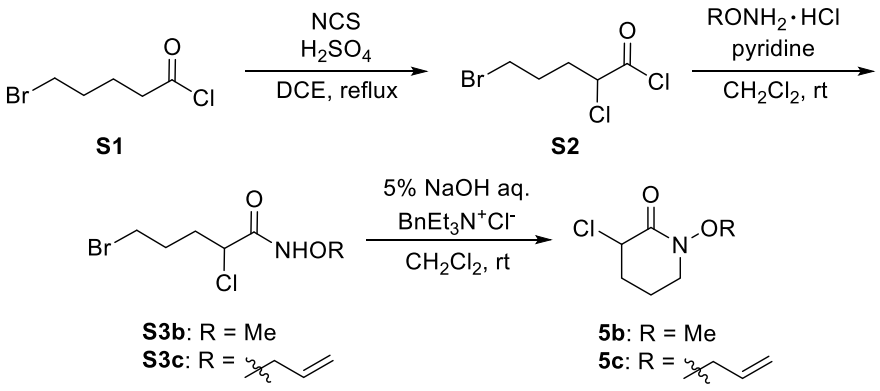
I. General Information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Flash column chromatography was performed using Silicycle silica gel (SiliaFlash® F60, 40-63 μm) or Biotage Automated Liquid Chromatography System Isolera One using Biotage SNAP KP-Sil 10g or 25g silica gel cartridges. Preparative thin-layer chromatography (preparative TLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60 F_{254}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, a JEOL ECZ400S, a Varian VNS AS 500 MHz or a Bruker AVANCE III HD 600 MHz operating at 300 MHz/75 MHz, 400 MHz/101 MHz, 500 MHz/126 MHz, or 600 MHz/150 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance or TMS as the internal standard. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), AB q (AB quartet), m (multiplet) and br (broad). Infrared (IR) spectra were recorded on a Perkin-Elmer SpectrumOne A spectrometer using NaCl plates or KBr pallets. High-resolution mass spectra (HRMS) were conducted on an FT-ESI mass analyzer. Melting points (uncorrected) were determined on BÜCHI M-565 apparatus. Grignard reagents and *i*-PrMgCl (2.0 M solution in THF) were purchased from Aldrich Chemical Co., Inc.. *n*-BuLi (1.6 M solution in hexane) and *N*-Chlorosuccinimide (NCS) were purchased from Nacalai Tesque, Inc.. The α-chloro-*N*-benzyloxylactam **5a** and *N*-benzyloxy-δ-lactam **9** were prepared according to literature.[1] The spectra data of these known compounds were identical with those reported in the literatures, respectively.

[1] N. Takeda, Y. Kobori, K. Okamura, M. Yasui, M. Ueda, *Org. Lett.*, **2020**, *22*, 9740.

II. Experimental Section

General procedure for the preparation of α-chloro-*N*-alkoxylactams 5

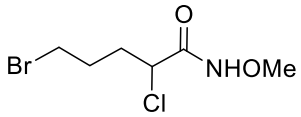


To a solution of 5-bromovaleryl chloride (**S1**) (3.99 g, 20 mmol) in 1,2-dicloroethane (40 mL) were added NCS (4.00 g, 30 mmol) and conc. H_2SO_4 (0.10 mL) at room temperature. After being stirred at reflux for 3 h, the reaction mixture was concentrated under reduced pressure. The crude product **S2** was used without the further purification.

To a solution of acyl chloride **S2** in CH_2Cl_2 (60 mL) were added *O*-alkoxyamine·HCl (20 mmol) and pyridine (3.24 mL, 40 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with AcOEt (300 mL). The mixture was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product **S3** was used without the further purification.

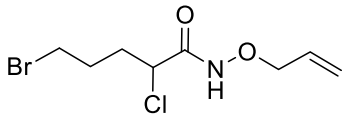
Spectral data were observed after purifying a small amount of sample.

5-Bromo-2-chloro-*N*-(methoxy)pentanamide (S3a)



A colorless oil. IR (neat) ν_{max} 3157, 2968, 1674 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.51-9.40 (m, 1H), 4.35 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.82 (s, 3H), 3.48-3.43 (m, 2H), 2.33-2.27 (m, 1H), 2.18-1.98 (m, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.0, 64.5, 57.1, 33.7, 32.2, 28.8; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_6H_{11}O_2N^{79}Br^{35}ClNa$ 265.9556; Found 265.9553.

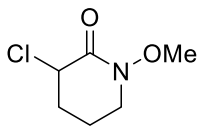
5-Bromo-2-chloro-*N*-(2-propen-1-yloxy)pentanamide (S3b)



A colorless oil. IR (neat) ν_{max} 3156, 2966, 1673 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.04-5.94 (m, 1H), 5.41-5.35 (m, 2H), 4.48-4.33 (m, 3H), 3.47-3.40 (m, 2H), 2.31-1.95 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.0, 131.5, 121.5, 77.5, 56.8, 33.6, 32.2, 28.8; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_8H_{13}O_2N^{79}Br^{35}ClNa$ 291.9709; Found 291.9711.

To a solution of the crude (**S3)** in CH_2Cl_2 (80 mL) were added 5% NaOH aq. (20 mL) and benzyltriethylammonium chloride (368.0 mg, 1.6 mmol) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was neutralized with 3 M HCl until pH = 7. The reaction mixture was diluted with AcOEt (400 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 1/1 to 1/3) to give α-chloro-*N*-alkoxylactams **5b** and **5c**.

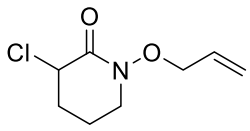
3-Chloro-1-methoxy-2-piperidinone (5b)



O-Methoxyamine·HCl (1.67 g, 20 mmol) was used. A colorless solid; 1.10 g, 34 % yield (3 steps). mp 42-43 °C; IR (KBr) ν_{max} 1678 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.49 (s, 1H), 3.81-3.54 (m, 5H), 2.44-1.94 (m, 4H); ^{13}C-NMR

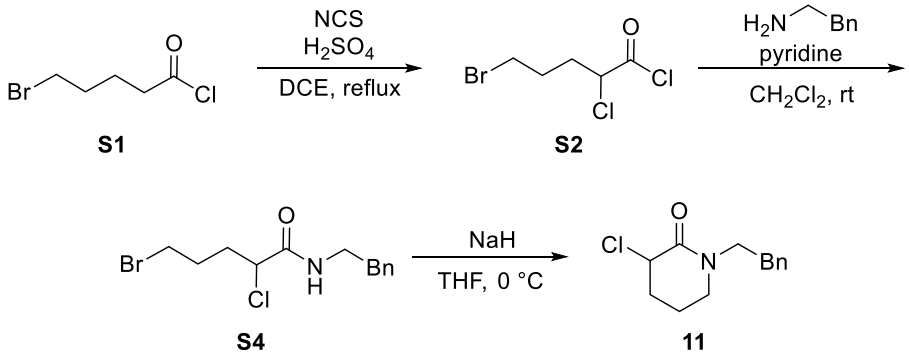
(101 MHz, $CDCl_3$) δ 163.1, 60.7, 55.4, 48.6, 30.5, 19.0; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_6H_{10}O_2N^{35}ClNa$ 186.0293; Found 186.0292.

3-Chloro-1-(2-propen-1-yloxy)-2-piperidinone (5c)

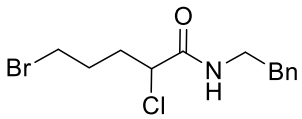


O-Allyloxyamine·HCl (2.59 g, 20 mmol) was used. A colorless oil; 0.97 g, 26 % yield (3 steps). IR (neat) ν_{max} 1679 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.06-5.95 (m, 1H), 5.41-5.31 (m, 2H), 4.47-4.43 (m, 3H), 3.68-3.57 (m, 2H), 2.35-2.11 (m, 3H), 1.93-1.90 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 163.6, 131.6, 121.0, 74.5, 55.5, 50.4, 30.4, 18.9; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_8H_{12}O_2N^{35}ClNa$ 212.0449; Found 212.0448.

Procedure for the preparation of α-chloro-δ-lactam 11



5-Bromo-2-chloro-*N*-(2-phenylethyl)pentanamide (S4)

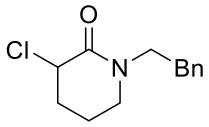


To a solution of 5-bromovaleryl chloride (**S1**) (1.99 g, 10 mmol) in 1,2-dicloroethane (20 mL) were added NCS (2.00 g, 15 mmol) and conc. H_2SO_4 (0.050 mL) at room temperature. After being stirred at reflux for 2 h, the reaction mixture was concentrated under reduced pressure. The crude product **S2** was used without the further purification.

To a solution of acyl chloride **S2** in CH_2Cl_2 (25 mL) were added phenethylamine (1.26 mL, 10 mmol) and pyridine (1.61 mL, 20 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with AcOEt (200 mL). The mixture was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 4/1 to 2/1) to give α-chloro-*N*-phenylethylactam **11** (1.76 g, 55%, 2 steps) as a yellow oil. IR (neat) ν_{max} 3306, 3014, 1663 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.16 (m, 5H), 6.64 (s, 1H), 4.35-4.23 (m, 1H), 3.62-3.36 (m, 4H), 2.90-2.79 (m, 2H), 2.27-1.85 (m, 4H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.2, 138.2, 128.7, 128.6, 126.6, 60.2, 41.0, 35.4, 34.1, 32.3, 28.9; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for

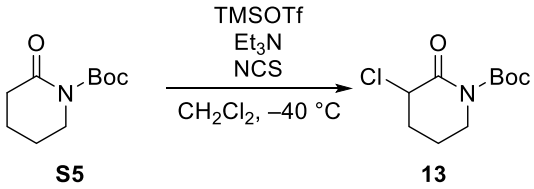
$C_{13}H_{17}ON^{79}Br^{35}ClNa$ 340.0074; Found 340.0077.

3-Chloro-1-(2-phenylethyl)-2-piperidinone (11)



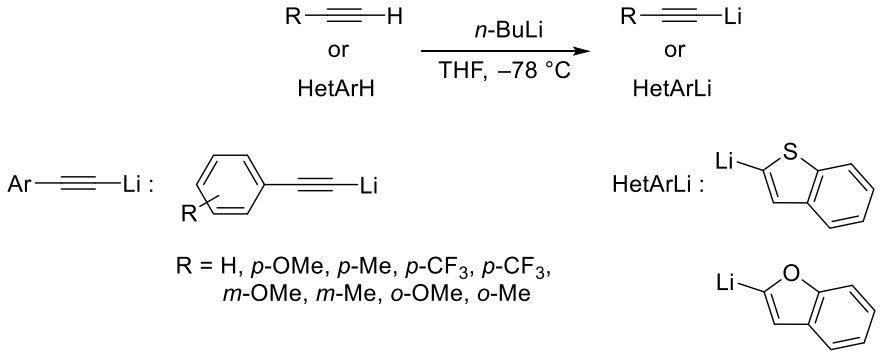
To a solution of **S4** (1.59 g, 5.0 mmol) in THF (50 mL) was slowly added NaH (600 mg, 15 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 3/1 to 1/1) to give *N*-phenylethyllactam **11 (**1.15 g, 97%) as a colorless oil. IR (neat) ν_{max} 1651 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 4.42 (t, *J* = 4.6 Hz, 1H), 3.71-3.64 (m, 1H), 3.46-3.38 (m, 1H), 3.15-3.04 (m, 2H), 2.95-2.84 (m, 2H), 2.20-2.01 (m, 3H), 1.70-1.64 (m, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 165.6, 138.7, 128.8, 128.4, 126.4, 54.9, 49.9, 48.6, 33.1, 30.9, 18.5; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{16}ON^{35}ClNa$ 260.0813; Found 260.0811.

1,1-Dimethylethyl 3-chloro-2-oxo-1-piperidinecarboxylate (13)



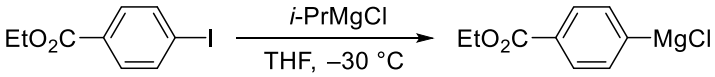
To a solution of 1-(*tert*-butoxycarbonyl)-2-piperidinone (**S8**) (2.0 g, 10.0 mmol) in CH_2Cl_2 (60 mL) were added dropwise Et_3N (5.8 mL, 40 mmol) and TMSOTf (2.1 mL, 12 mmol) at –20 °C under an argon atmosphere. After being stirred at the same temperature for 15 min, the reaction mixture was stirred at 0 °C for 45 min. Then the reaction mixture was cooled to –78 °C, NCS (2.0 g, 15 mmol) was added at the same temperature. After being stirred at –40 °C for 1.5 h, the reaction mixture was quenched with saturated NH_4Cl (60 mL) and warm up to room temperature for 15 min. The mixture was extracted with AcOEt. The organic phase was washed with brine (x2), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 5/1 to 1/1) to afford α-chloro-*N*-Boc-lactam **13** (1.9 g, 83%) as a colorless solid. mp 93-94 °C; IR (KBr) ν_{max} 1757, 1672, 1318, 1157 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.49 (t, *J* = 5.6 Hz, 1H), 3.84-3.78 (m, 1H), 3.64 (dd, *J* = 8.4, 4.9 Hz, 1H), 2.35-2.13 (m, 3H), 1.90 (br m, 1H), 1.53 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 166.8, 152.6, 83.6, 56.9, 45.8, 30.8, 27.9, 19.4; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{10}H_{16}O_3N^{35}ClNa$ 256.0711; Found 256.0713.

General procedure for the preparation of organolithium reagent (0.26 M solution)



To a solution of terminal alkyne or HetArH (1.80 mmol) in THF (5.6 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 1.1 mL, 1.80 mmol) at –78 °C under an argon atmosphere. The resulting mixture was stirred at the same temperature for 30 min, and was used directly in the following reaction.

General procedure for the preparation of 4-(ethoxycarbonyl)phenylmagnesium chloride reagent (0. 30 M solution)

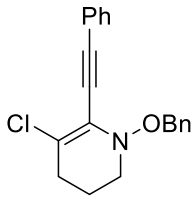


To a solution of 4-iodobenzoic acid ethyl ester (0.25 mL, 1.5 mmol) in THF (4.21 mL) was added dropwise *i*-PrMgCl (2.0 M in THF, 0.79 mL, 1.58 mmol) at –30 °C under an argon atmosphere. The resulting mixture was stirred at the same temperature for 30 min, and was used directly in the following reaction.

General procedure for sequential nucleophilic addition/dehydration of α-chloro-*N*-alkoxylactam 5 with organometallic reagents

To a solution of α-chloro-*N*-alkoxylactam **5a** (47.9 mg, 0.20 mmol) in THF (2.0 mL) was slowly added organolithium reagent (0.26 M in THF, 1.5 mL, 0.40 mmol) or Grignard reagent (1.0 M in THF, 0.40 mL, 0.40 mmol) at –78 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with 1 M HCl (2.5 mL) and diluted with $CHCl_3$ (5 mL), then warm up to room temperature for 45 min. The mixture was extracted with $CHCl_3$ (20 mL x 3). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage Isolera One) or preparative TLC (PTLC) to afford β-chloroenamines **8** and **7**.

3-Chloro-2-(2-phenylethynyl)-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8aa)

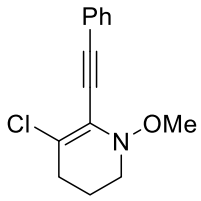


57.4 mg, 89% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2222 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.43-7.24 (m, 8H), 4.99 (s, 2H), 3.22-3.18 (m, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.92-1.84 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.7, 131.7, 129.1, 128.6, 128.5, 128.3, 128.3, 128.0, 127.4, 122.8, 93.3, 83.7, 76.6, 51.2, 31.7, 19.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{20}H_{19}ON^{35}Cl$ 324.1150; Found 324.1148.

Nucleophilic addition/dehydration of *N*-alkoxylactam 5a with PhC≡CLi on 3.0 mmol scale

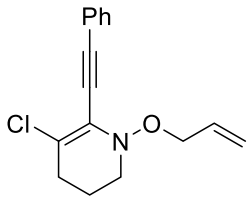
To a solution of *N*-alkoxylactam **5a** (719.0 mg, 3.0 mmol) in THF (30 mL) was slowly added PhC≡CLi (0.26 M in THF, 22.5 mL, 6.0 mmol) at –78 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with 1 M HCl (37.5 mL) and diluted with $CHCl_3$ (75 mL), then warm up to room temperature for 45 min. The mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 10/1 to 3/1) to afford β-chloroenamine **8aa** (864.6 mg, 89% yield) as a yellow oil.

3-Chloro-2-(2-phenylethynyl)-1,4,5,6-tetrahydro-1-(methoxy)pyridine (8ab)



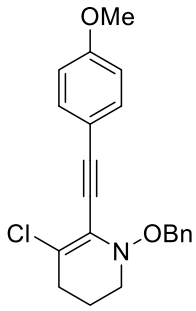
The reaction of **5b** (32.7 mg, 0.20 mmol) gave **8ab** (27.9 mg, 56% yield). Purification by preparative TLC (hexane/AcOEt = 4/1); A yellow oil; IR (neat) ν_{max} 2221 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.49 (m, 2H), 7.35-7.31 (m, 3H), 3.76 (s, 3H), 3.26-3.22 (m, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 1.93-1.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 131.7, 128.5, 128.3, 127.5, 122.7, 93.0, 83.5, 61.7, 50.3, 31.7, 19.2; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{15}ON^{35}Cl$248.0837; Found 248.0840.
One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

3-Chloro-2-(2-phenylethynyl)-1,4,5,6-tetrahydro-1-(2-propen-1yloxy)pyridine (8ac)



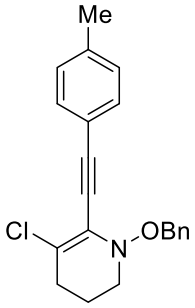
The reaction of **5c** (38.0 mg, 0.20 mmol) gave **8ac** (27.4 mg, 50% yield). Purification by preparative TLC (hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2222 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54-7.48 (m, 2H), 7.36-7.31 (m, 3H), 6.11-5.98 (m, 1H), 5.35-5.20 (m, 2H), 4.46 (dt, *J* = 6.2, 1.2 Hz, 2H), 3.26-3.23 (m, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 1.95-1.87 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.9, 131.6, 128.5, 128.3, 127.6, 122.8, 118.5, 93.2, 83.7, 75.3, 51.2, 31.7, 19.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{17}ON^{35}Cl$ 274.0991; Found 274.0994.
One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

3-Chloro-2-[2-(4-methoxyphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8ba)



61.6 mg, 87% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2220 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.22 (m, 7H), 6.83 (d, *J* = 11.0 Hz, 2H), 4.97 (s, 2H), 3.80 (s, 3H), 3.20-3.17 (m, 2H), 2.41 (t, *J* = 6.5 Hz, 2H), 1.91-1.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.8, 136.8, 133.1, 129.1, 128.8, 128.3, 128.0, 126.7, 114.9, 113.9, 93.4, 82.5, 76.6, 55.3, 51.2, 31.6, 19.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{21}O_2N^{35}Cl$ 354.1256; Found 354.1250.

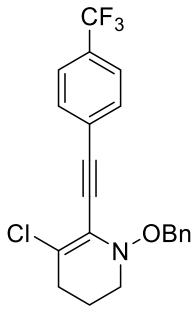
3-Chloro-2-[2-(4-methylphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8ca)



55.6 mg, 82% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2220 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43-7.39 (m, 4H), 7.34-7.25 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.98 (s, 2H), 3.22-3.18 (m, 2H), 2.44-2.36 (m, 5H), 1.92-1.84 (m, 2H)；^{13}C-NMR (75 MHz, $CDCl_3$) δ 138.7, 136.8, 131.5, 129.1, 128.7, 128.3, 128.0, 127.0, 119.7, 93.5, 83.1, 76.6, 51.2, 31.6, 21.5, 19.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{21}ON^{35}Cl$ 338.1309; Found 338.1305.

One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

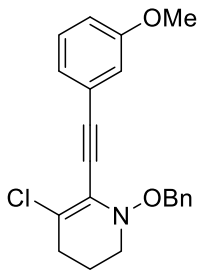
3-Chloro-1,4,5,6-tetrahydro-2-[2-[(4-trifluoromethyl)phenyl]ethynyl]-1-(phenylmethoxy)pyridine (8da)



0

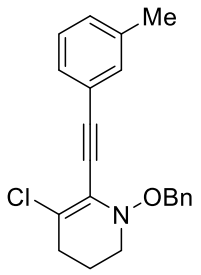
60.3 mg, 77% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2225 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.42-7.25 (m, 5H), 4.97 (s, 2H), 3.23-3.19 (m, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 1.94-1.88 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 136.7, 131.9, 130.2 (C-F, $^2J_{C\text{-}F}$ = 32.5 Hz), 129.0, 128.6, 128.4, 128.3, 128.2, 126.6, 125.3 (C-F, $^3J_{C\text{-}F}$ = 3.5 Hz), 123.9 (C-F, $^1J_{C\text{-}F}$ = 271.0 Hz), 91.7, 86.1, 76.6, 51.1, 31.7, 19.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{18}ON^{35}ClF_3$ 392.1028; Found 392.1021.

3-Chloro-2-[2-(3-methoxyphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8ea)



45.9 mg, 65% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2214 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.35-7.21 (m, 4H), 7.11 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.02 (q, *J* = 1.3 Hz, 1H), 6.90 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.98 (s, 2H), 3.79 (s, 3H), 3.22-3.19 (m, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.92-1.84 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.3, 136.7, 129.4, 129.1, 128.6, 128.3, 128.1, 127.5, 124.2, 123.7, 116.4, 115.2, 93.2, 83.5, 77.4, 55.3, 51.2, 31.7, 19.3; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{21}O_2N^{35}Cl$ 354.1252; Found 354.1257.

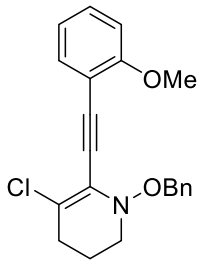
3-Chloro-2-[2-(3-methylphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8fa)



58.8 mg, 87% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2213 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.35-7.19 (m, 6H), 7.15 (d, *J* = 7.7 Hz, 1H), 4.99 (s, 2H), 3.22-3.18 (m, 2H), 2.45-2.34 (m, 5H), 1.93-1.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.7, 136.6, 132.0, 129.3, 128.9, 128.6, 128.1, 128.0, 127.9, 127.1, 122.4, 93.5, 83.3, 76.6, 51.4, 31.8, 21.4, 19.6; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{21}ON^{35}Cl$ 338.1306; Found 338.1309.

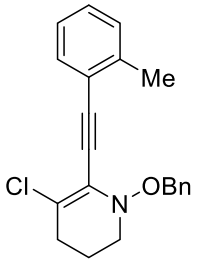
One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

3-Chloro-2-[2-(2-methoxyphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8ga)



62.5 mg, 88% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2221 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49-7.42 (m, 3H), 7.34-7.25 (m, 4H), 6.94-6.86 (m, 2H), 5.06 (s, 2H), 3.81 (s, 3H), 3.21-3.17 (m, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.91-1.83 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 160.2, 137.0, 133.5, 130.0, 129.1, 128.9, 128.2, 127.9, 126.8, 120.4, 112.2, 110.6, 89.9, 87.7, 76.6, 55.6, 51.4, 31.7, 19.4; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{21}O_2N^{35}Cl$ 354.1252; Found 354.1257.

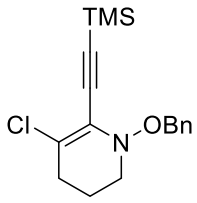
3-Chloro-2-[2-(2-methylphenyl)ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (8ha)



60.8 mg, 90% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2219 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47-7.39 (m, 3H), 7.35-7.14 (m, 6H), 5.01 (s, 2H), 3.22-3.18 (m, 2H), 2.51-2.41 (m, 5H), 1.93-1.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.2, 136.5, 131.8, 129.3, 128.8, 128.6, 128.4, 128.1, 127.9, 127.2, 125.3, 122.4, 92.3, 87.6, 76.6, 51.3, 31.9, 21.1, 19.5; HRMS (ESI) *m*/*z*: [M

+ H]$^+$ Calcd for $C_{21}H_{21}ON^{35}Cl$ 338.1303; Found 338.1308.

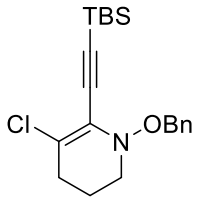
3-Chloro-1,4,5,6-tetrahydro-2-[2-(trimethylsilyl)ethynyl]-1-(phenylmethoxy)pyridine (8ia)



59.2 mg, 92% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2160 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 4.93 (s, 2H), 3.16-3.12 (m, 2H), 2.36 (t, *J* = 6.5 Hz, 2H), 1.87-1.79 (m, 2H), 0.25 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.5, 128.8, 128.1, 127.84, 127.77, 99.1, 98.5, 76.6, 51.2, 31.7, 19.4, 0.07; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{17}H_{23}ON^{35}ClSi$ 320.1232; Found 320.1235.

One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

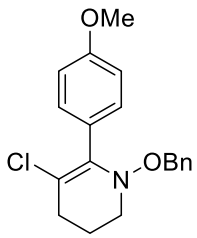
3-Chloro-2-[2-[(1,1-dimethylethyl)dimethylsilyl]ethynyl]-1,4,5,6-tetrahydro-1-(phenylmethoxy) pyridine (8ja)



64.5 mg, 89% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 5/1); A yellow oil; IR (neat) ν_{max} 2160 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 4.93 (s, 2H), 3.15-3.12 (m, 2H), 2.36 (t, *J* = 6.5 Hz, 2H), 1.84-1.81 (m, 2H), 1.00 (s, 9H), 0.18 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.5, 128.8, 128.3, 128.1, 127.8, 99.2, 97.6, 76.6, 51.2, 31.8, 26.3, 19.5, 16.9, -4.4; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{20}H_{29}ON^{35}ClSi$ 362.1702; Found 362.1698.

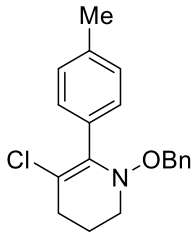
One of carbons (C*sp*^{2}) overlapped with other carbons (C*sp*^{2}) in ^{13}C NMR spectrum.

3-Chloro-2-(4-methoxy)phenyl-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7b)



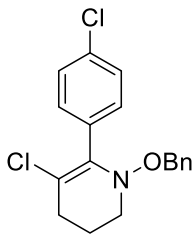
4-MethoxyphenylMgBr (0.50 M in THF, 0.80 mL, 0.40 mmol) was used. 54.9 mg, 83% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 10/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.46 (m, 3H), 7.24-7.19 (m, 2H), 6.97-6.89 (m, 4H), 4.46 (s, 2H), 3.83 (s, 3H), 3.33-3.29 (m, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 1.93-1.87 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.3, 142.0, 136.6, 131.3, 128.2, 127.8, 127.7, 120.3, 114.1, 113.0, 75.9, 55.2, 51.2, 32.5, 19.2; HRMS (ESI) *m*/*z*: [M + H]$^+$ Calcd for $C_{19}H_{21}O_2N^{35}Cl$ 330.1259; Found 330.1254.

3-Chloro-2-(4-methyl)phenyl-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7c)



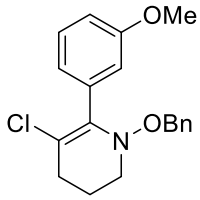
28.2 mg, 45% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.22-7.17 (m, 5H), 6.94-6.90 (m, 2H), 4.44 (s, 2H), 3.33-3.29 (m, 2H), 2.45-2.39 (m, 5H), 1.94-1.86 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.4, 137.8, 136.6, 133.7, 129.9, 128.8, 128.4, 128.1, 127.8, 120.4, 76.0, 51.3, 32.5, 21.4, 19.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}ON^{35}Cl$ 314.1308; Found 314.1306.

3-Chloro-2-(4-chloro)phenyl-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7d)



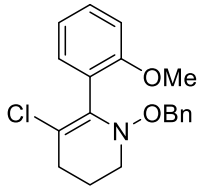
4-ChlorophenylMgBr (1.0 M in Et_2O, 0.40 mL, 0.40 mmol) was used. 35.5 mg, 53% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.35-7.30 (m, 2H), 7.24-7.18 (m, 3H), 6.95-6.92 (m, 2H), 4.44 (s, 2H), 3.33-3.30 (m, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 1.95-1.87 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.4, 136.3, 135.0, 133.7, 131.4, 128.7, 128.2, 127.9, 127.9, 121.5, 75.8, 51.0, 32.5, 19.2; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{18}ON^{35}Cl_2$ 334.0762; Found 334.0759.

3-Chloro-2-(3-methoxy)phenyl-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7f)



44.0 mg, 67% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 10/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 1H), 7.21-7.12 (m, 5H), 6.95-6.89 (m, 3H), 4.47 (s, 2H), 3.82 (s, 3H), 3.35-3.31 (m, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 1.95-1.87 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.0, 142.3, 137.9, 136.5, 128.8, 128.6, 128.2, 127.9, 122.6, 120.8, 115.2, 114.2, 76.0, 55.3, 51.3, 32.5, 19.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}O_2N^{35}Cl$ 330.1256; Found 330.1256.

3-Chloro-2-(2-methoxy)phenyl-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7g)

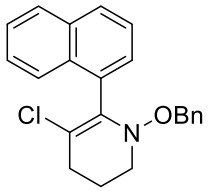


44.1 mg, 68% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A white solid; mp 105-107 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.4, 1.7 Hz, 2H), 7.21 (m, 3H), 7.01-6.93 (m, 4H), 4.37 and 4.34 (ABq, *J* = 10.2 Hz, each 1H), 3.84 (s, 3H), 3.40-3.25 (m, 2H), 2.54-2.34 (m, 2H), 1.97-1.89 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 157.8, 139.6, 136.6, 131.6, 129.5, 128.9, 128.1, 127.7, 125.7, 120.8, 120.1, 111.4, 75.8, 56.0, 51.5, 31.7, 19.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}O_2N^{35}Cl$ 330.1254; Found 330.1256.

Nucleophilic addition/dehydration of *N*-alkoxylactam 5a with *o*-$MeOC_6H_4MgBr$ on 3.0 mmol scale

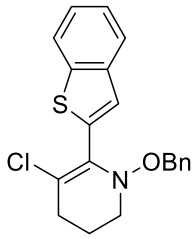
To a solution of *N*-alkoxylactam **5a** (719.0 mg, 3.0 mmol) in THF (30 mL) was slowly added *o*-$MeOC_6H_4MgBr$ (1.0 M in THF, 6.0 mL, 6.0 mmol) at –78 °C under an argon atmosphere. After being stirred at the same temperature for 1.5 h, the reaction mixture was quenched with 1 M HCl (37.5 mL) and diluted with $CHCl_3$ (75 mL), then warm up to room temperature for 15 min. The mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 10/1 to 5/1) to afford β-chloroenamine **7g** (662.8 mg, 67% yield) as a white solid.

3-Chloro-2-(1-naphthalenyl)-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7h)



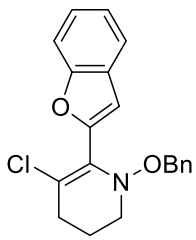
1-NaphthylMgBr (0.25 M in THF, 1.60 mL, 0.40 mmol) was used. 40.9 mg, 58% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06-8.02 (m, 1H), 7.87-7.80 (m, 2H), 7.56-7.43 (m, 4H), 7.13-7.02 (m, 3H), 6.66 (d, *J* = 7.8 Hz, 2H), 4.10 and 4.02 (ABq, *J* = 10.3 Hz, each 1H), 3.41-3.37 (m, 2H), 2.55-2.50 (m, 2H), 2.05-1.96 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.5, 136.3, 134.0, 133.4, 131.9, 128.8, 128.5, 128.3, 128.1, 127.9, 127.7, 126.0, 125.9, 125.6, 125.0, 121.1, 75.8, 51.7, 31.9, 19.9; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{21}ON^{35}Cl$ 350.1304; Found 350.1307.

2-(2-Benzo[*b*]thien-2-yl)-3-chloro-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7i)



52.1 mg, 73% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89-7.75 (m, 2H), 7.69 (s, 1H), 7.43-7.29 (m, 3H), 7.22-7.16 (m, 2H), 7.10-7.06 (m, 2H), 4.80 (s, 2H), 3.32-3.29 (m, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 1.98-1.90 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.7, 136.5, 136.3, 128.6, 128.2, 127.9, 126.2, 125.8, 124.9, 124.4, 123.8, 123.5, 122.4, 122.1, 75.8, 50.4, 33.0, 18.5; HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{20}H_{19}ON^{35}ClS$ 356.0870; Found 356.0868.

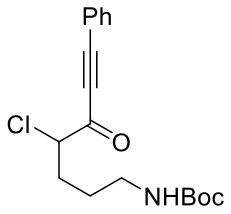
2-(2-Benzofuranyl)-3-chloro-1,4,5,6-tetrahydro-1-(phenylmethoxy)pyridine (7j)



33.4 mg, 57% yield. Purification by flash column chromatography (Biotage Isolera One, hexane/AcOEt = 20/1); A yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62-7.59 (m, 1H), 7.54-7.51 (m, 1H), 7.34-7.05 (m, 8H), 4.82 (s, 2H), 3.38-3.35 (m, 2H), 2.53 (t, *J* = 6.6 Hz, 2H), 2.00-1.92 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.1, 150.9, 136.4, 133.9, 128.7, 128.3, 128.2, 127.9, 125.4, 124.6, 122.8,

121.2, 111.3, 108.7, 75.7, 50.5, 32.9, 18.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}O_2N^{35}Cl$ 340.1100; Found 340.1098.

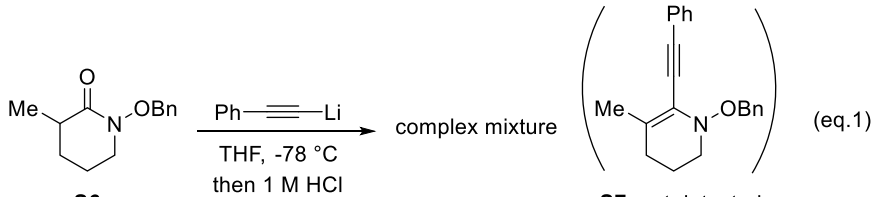
1,1-Dimethylethyl *N*-(4-chloro-7-phenyl-5-oxo-6-heptyn-1-yl)carbamate (14)



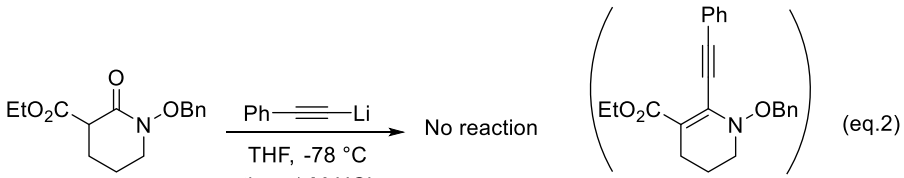
The reaction of *N*-Boc lactam **13** (46.7 mg, 0.20 mmol) gave **14** (48.8 mg, 73% yield). Purification by preparative TLC (hexane/AcOEt = 2/1); A colorless oil; IR (neat) ν_{max} 3360, 2205, 1682 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64-7.60 (m, 2H), 7.53-7.38 (m, 3H), 4.64 (s, 1H), 4.44 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.22-1.98 (m, 2H), 1.79-1.64 (m, 2H), 1.43 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.8, 155.9, 133.3, 131.3, 128.7, 119.3, 95.2, 85.5, 79.3, 64.1, 39.7, 31.1, 28.3, 26.5; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{22}O_3N^{35}ClNa$ 358.1180; Found 358.1187.

III. Additional experiments

(1) Substituent effects at the α-position of *N*-alkoxylactam

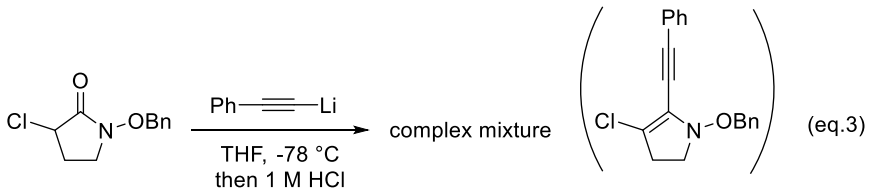


S6 **S7**: not detected

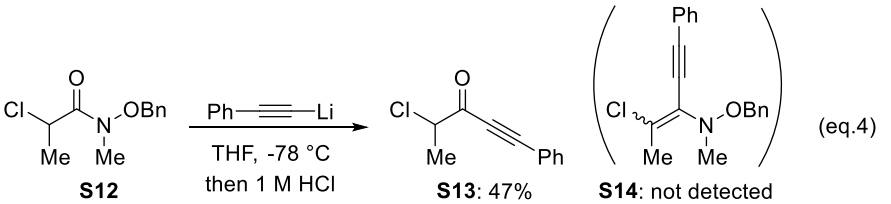


S8 **S9**: not detected

(2) Unsuccessful results utilizing *N*-alkoxy-γ-lactam and acyclic *N*-alkoxyamide

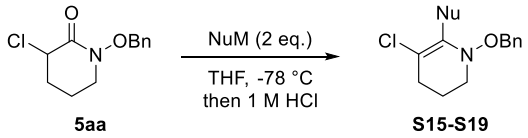


S10 **S11**: not detected

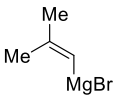
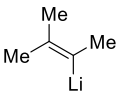
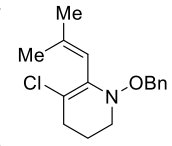
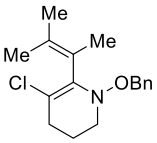
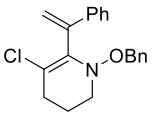
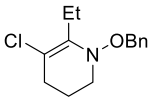
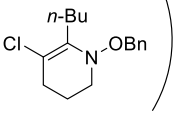


S12 **S13**: 47% **S14**: not detected

(3) Unsuccessful results utilizing other types of NuLi and NuMgBr

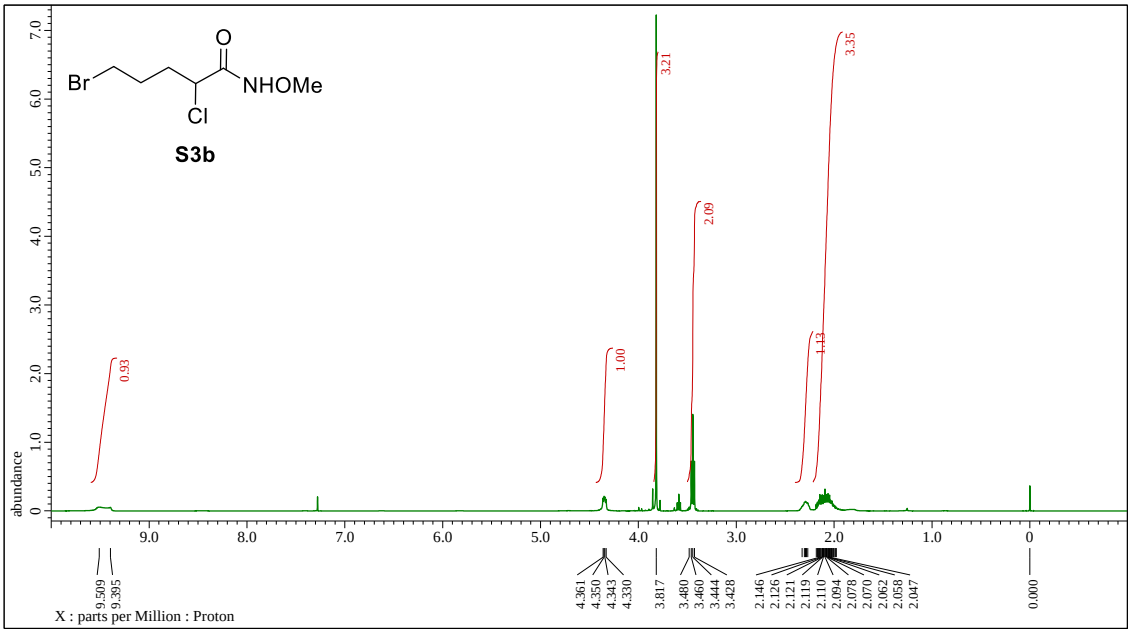


5aa **S15-S19**

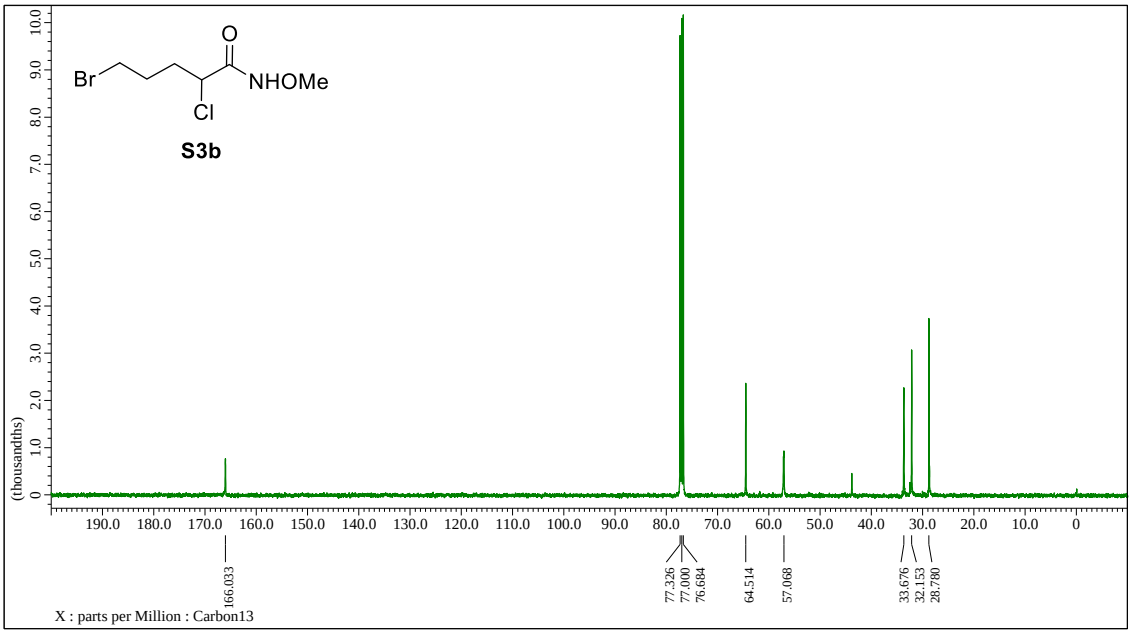
NuM				EtMgBr	*n*-BuLi
product	 **S15**: not detected	 **S16**: not detected	 **S17**: not detected	 **S18**: not detected	 **S19**: not detected

IV. NMR Spectral Data

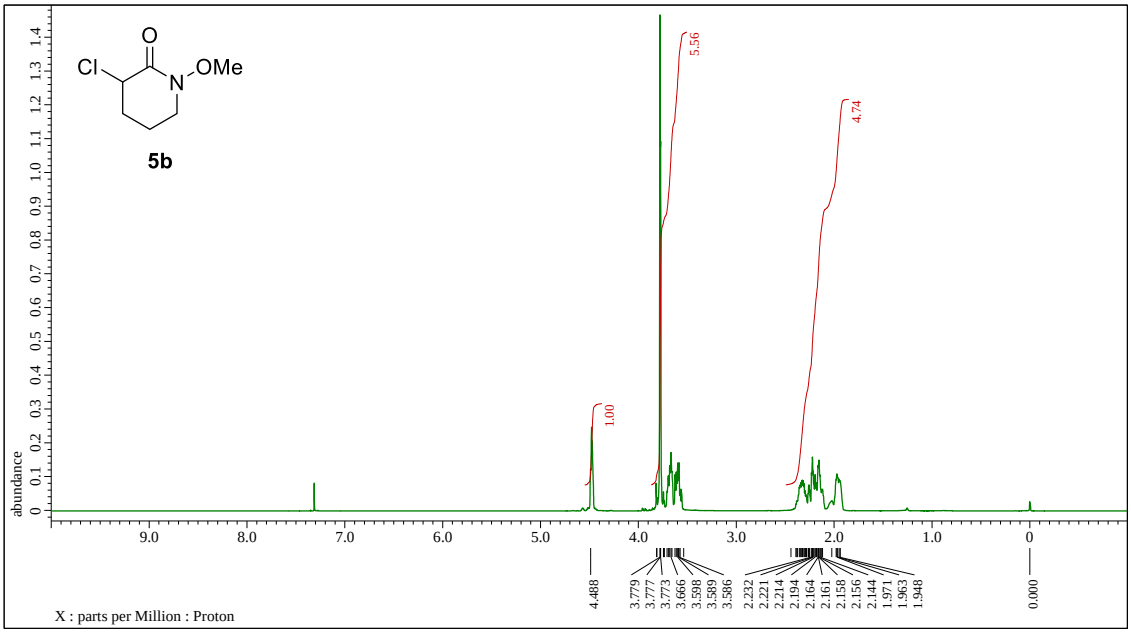
^{1}H-NMR (400 MHz, $CDCl_3$)



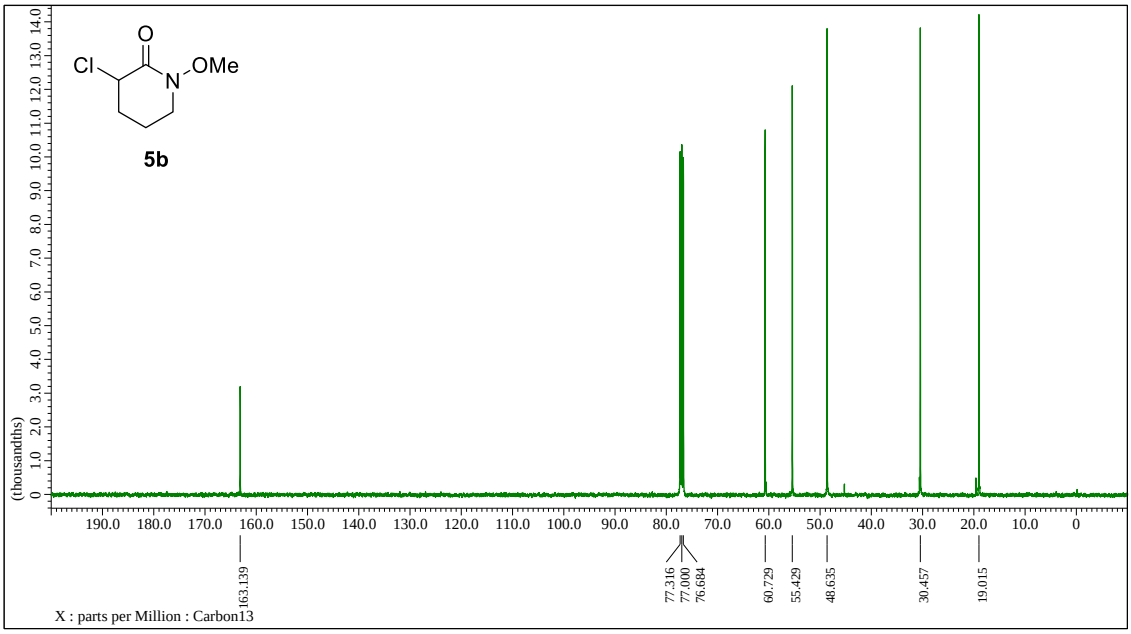
^{13}C-NMR (101 MHz, $CDCl_3$)



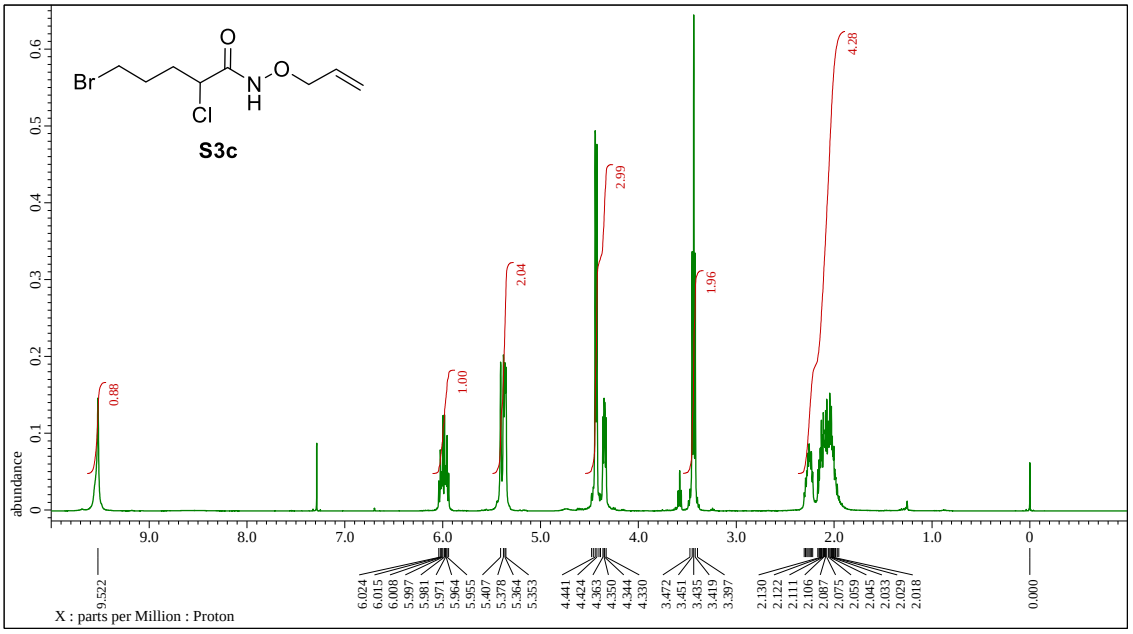
^{1}H-NMR (400 MHz, $CDCl_3$)



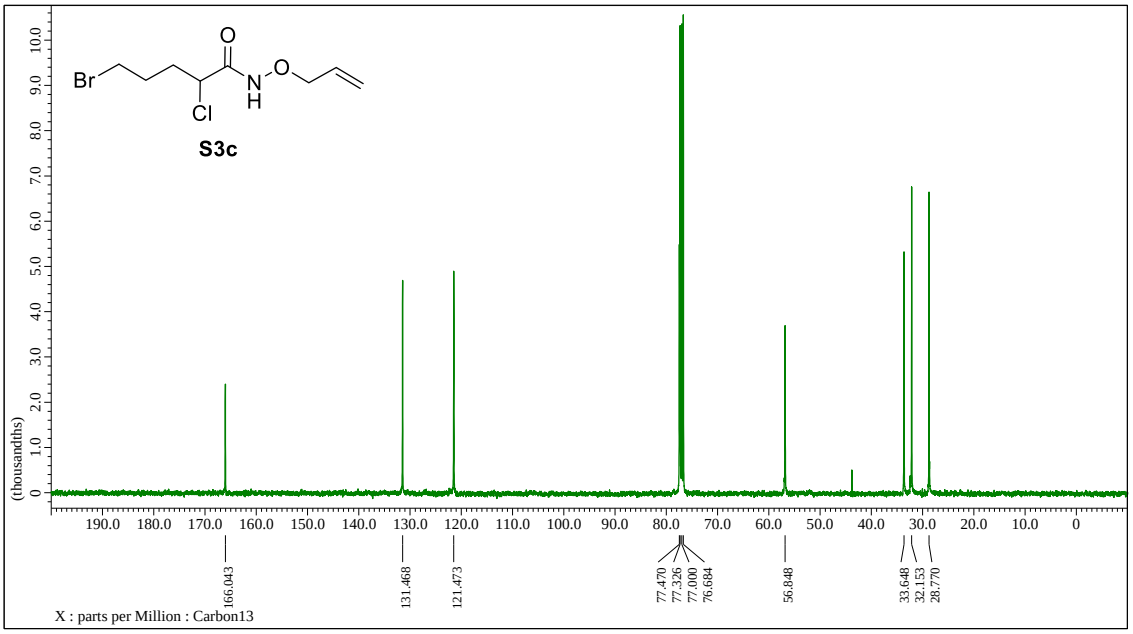
^{13}C-NMR (101 MHz, $CDCl_3$)



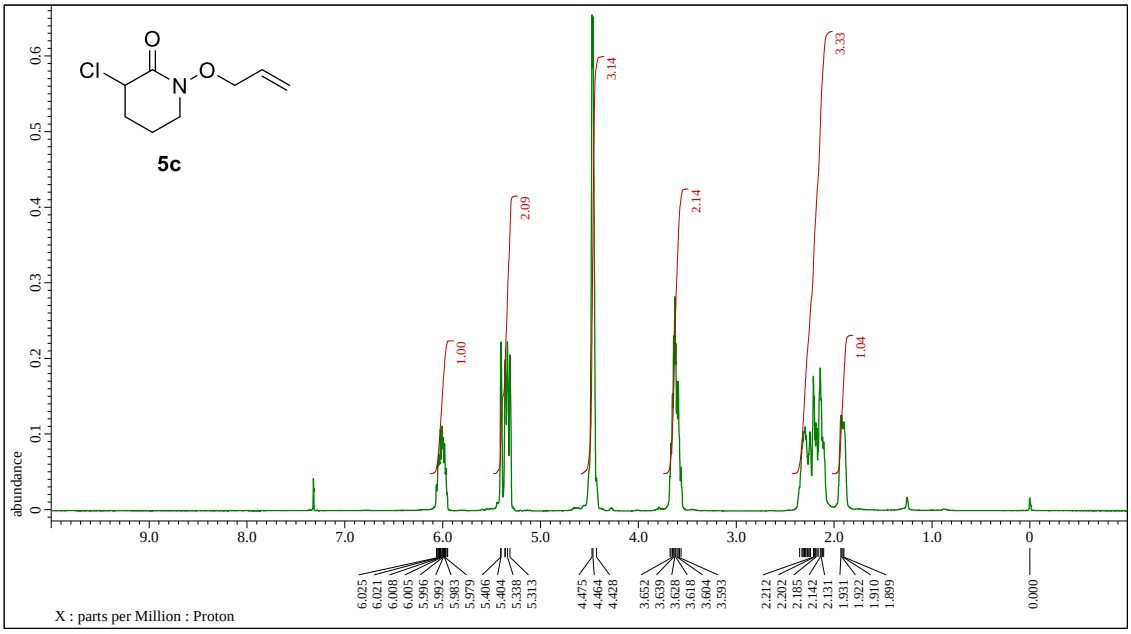
^{1}H-NMR (400 MHz, $CDCl_3$)



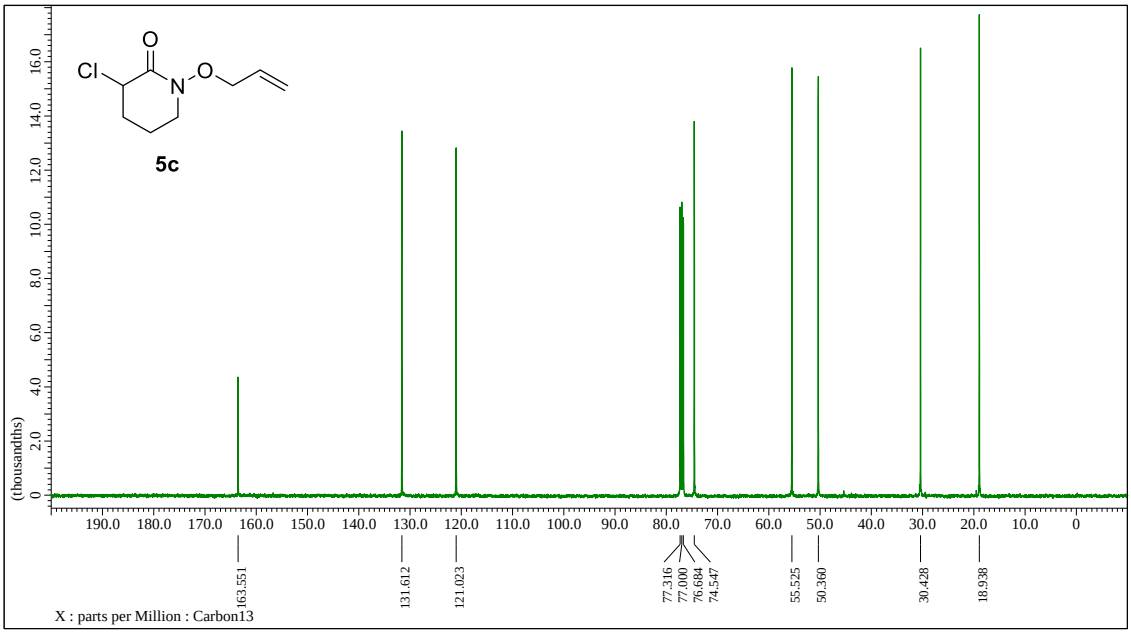
^{13}C-NMR (101 MHz, $CDCl_3$)



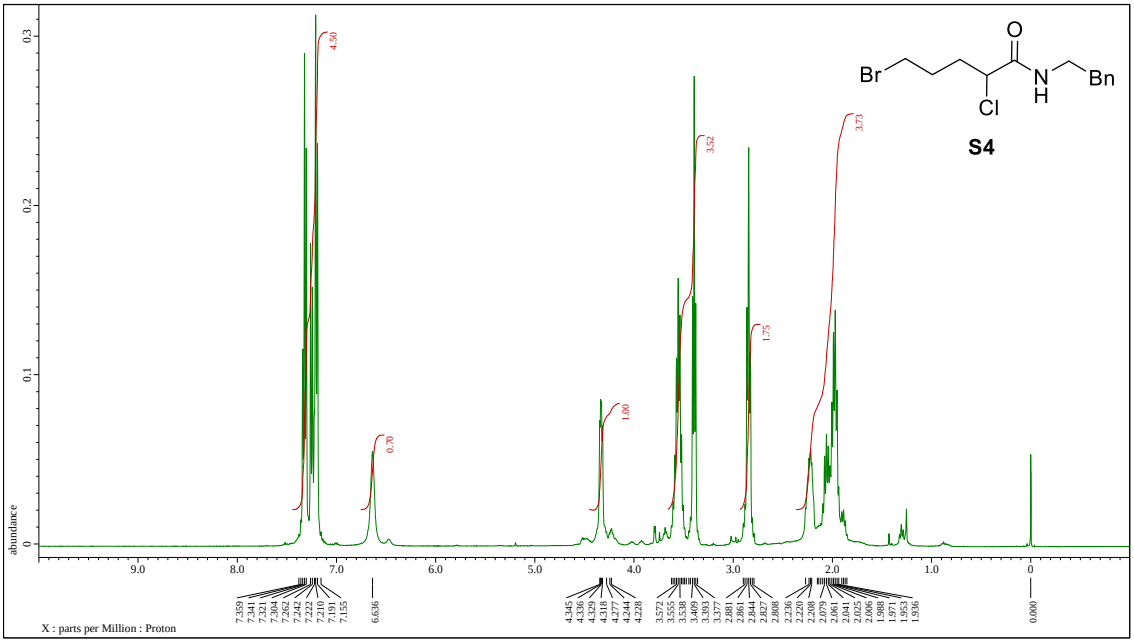
^{1}H-NMR (400 MHz, $CDCl_3$)



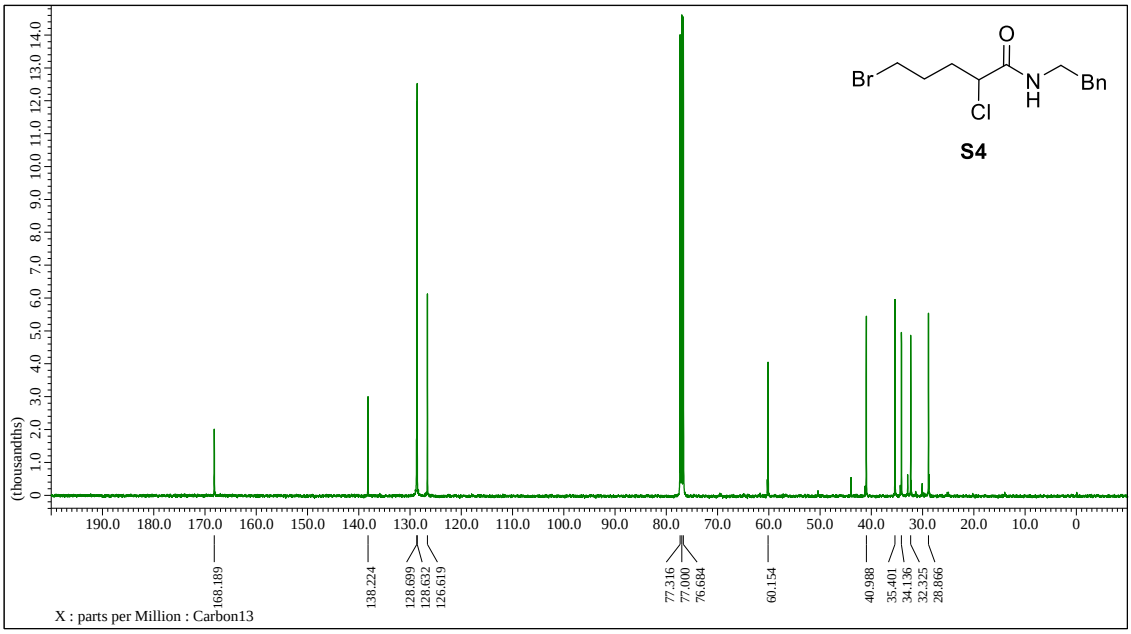
^{13}C-NMR (101 MHz, $CDCl_3$)



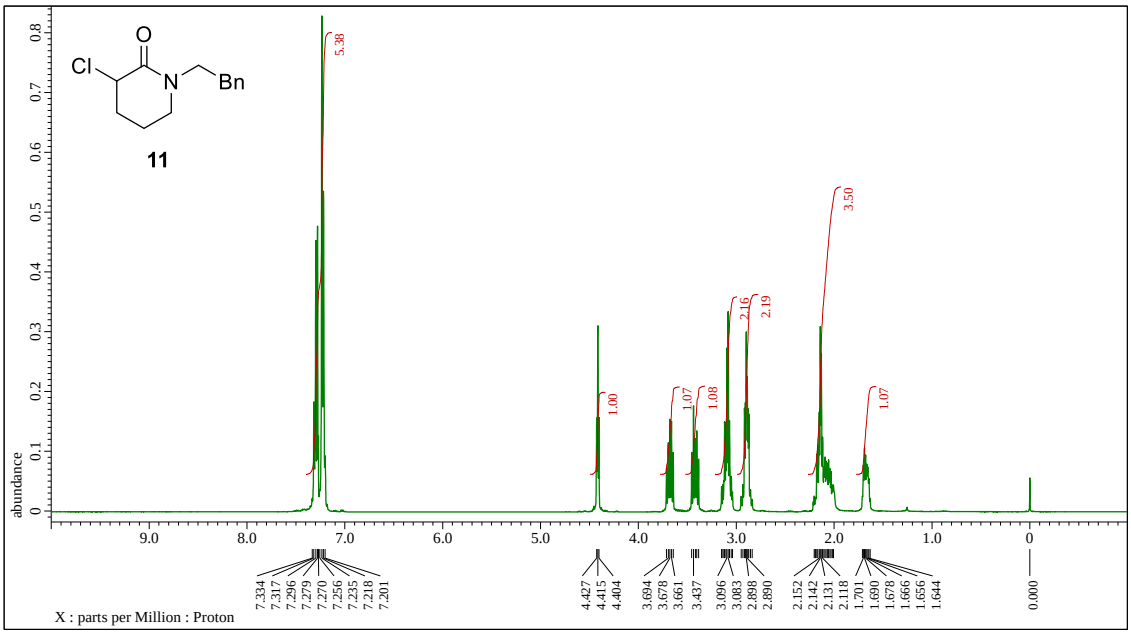
^{1}H-NMR (400 MHz, $CDCl_3$)



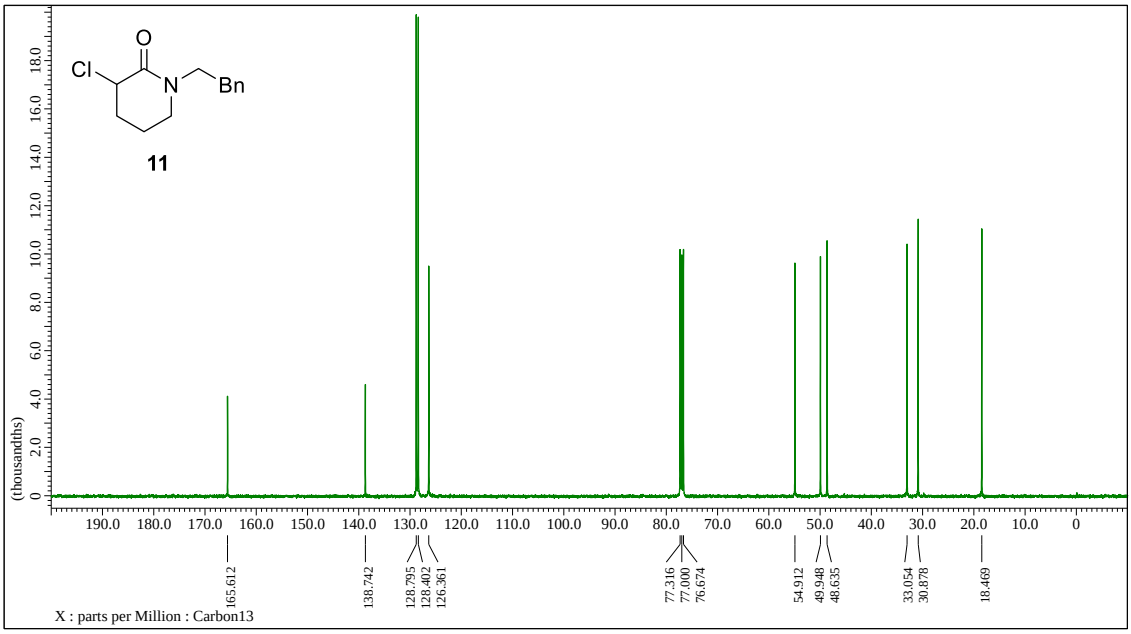
^{13}C-NMR (101 MHz, $CDCl_3$)



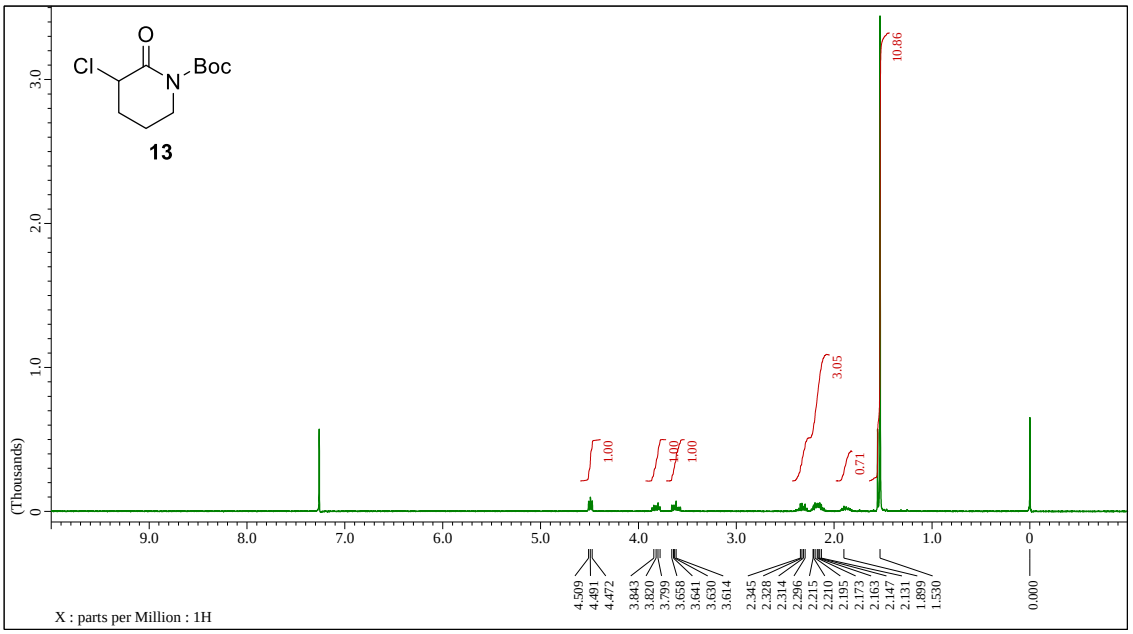
^{1}H-NMR (300 MHz, $CDCl_3$)



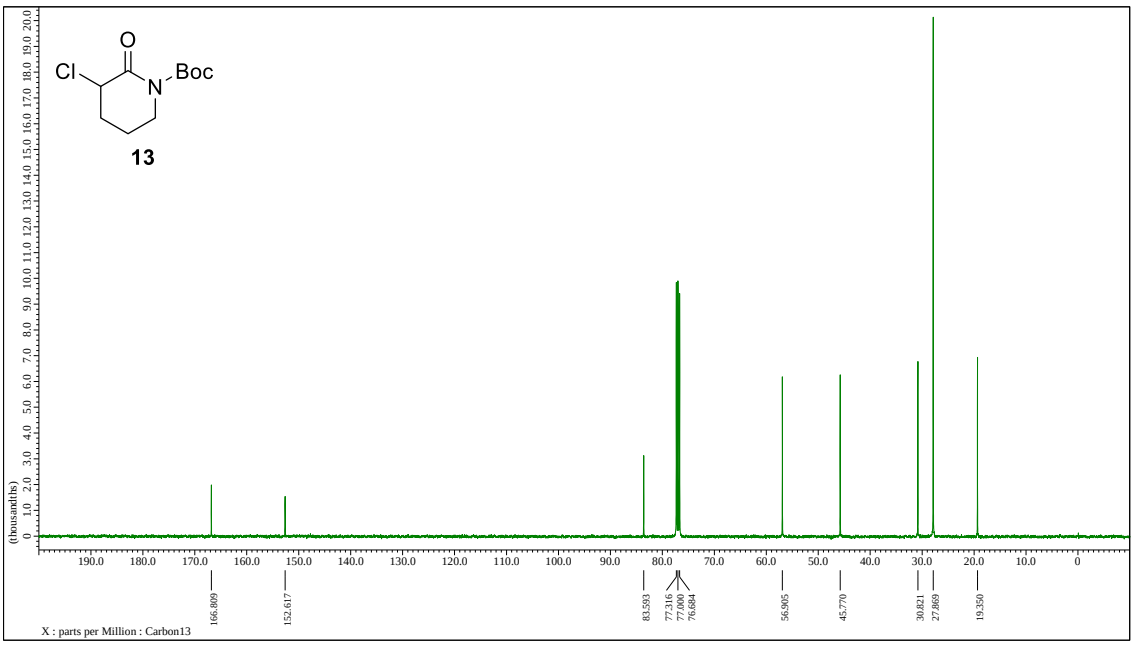
^{13}C-NMR (101 MHz, $CDCl_3$)



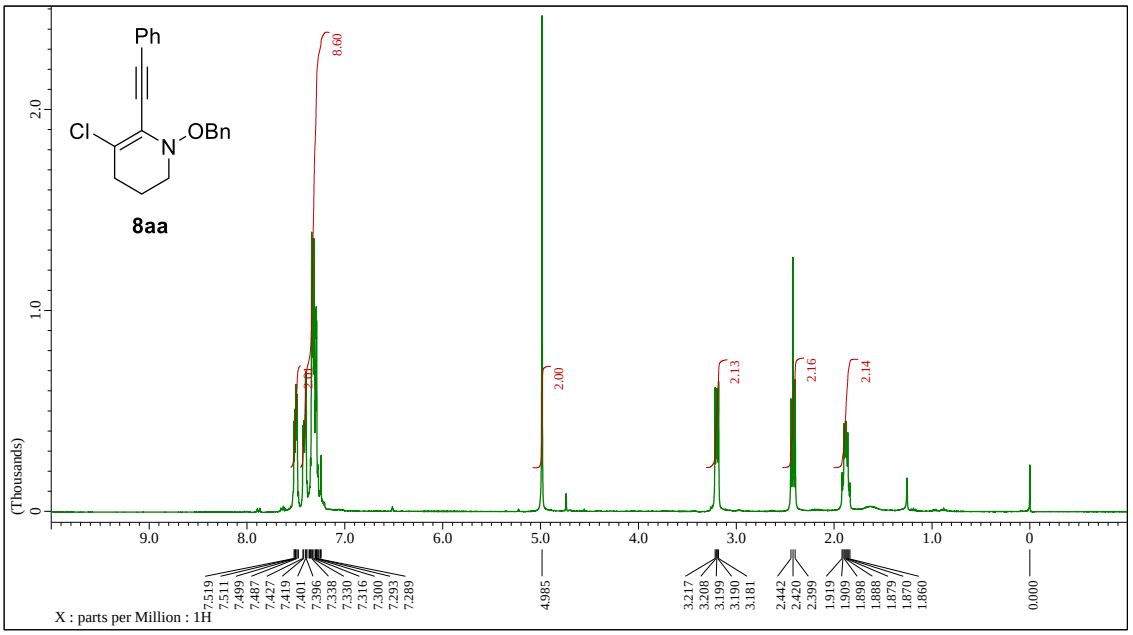
^{1}H-NMR (300 MHz, $CDCl_3$)



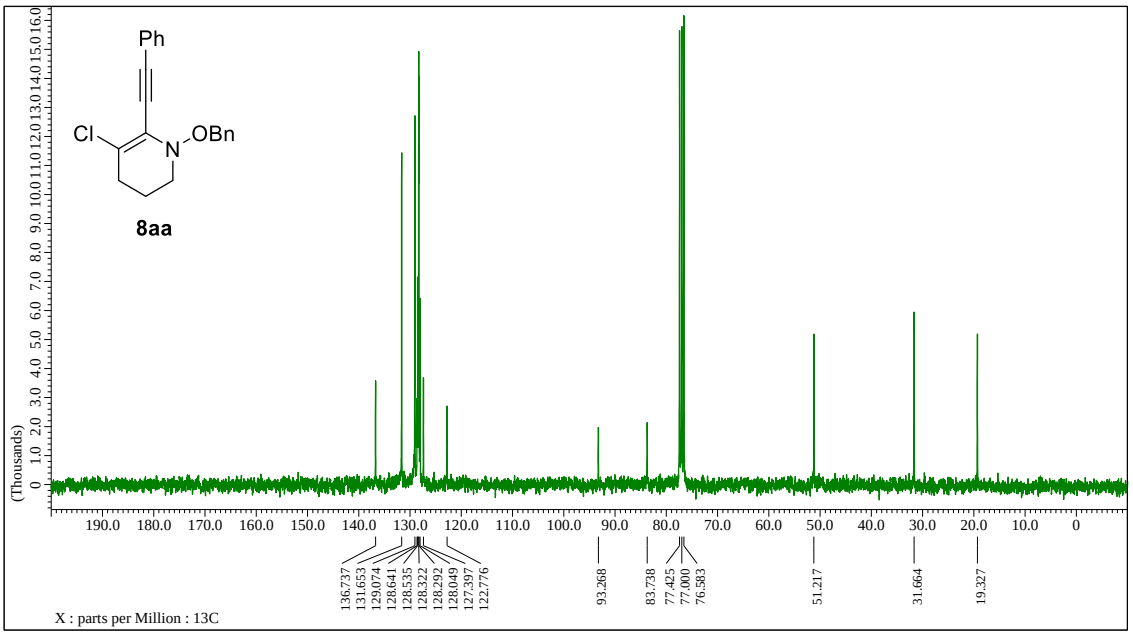
^{13}C-NMR (101 MHz, $CDCl_3$)



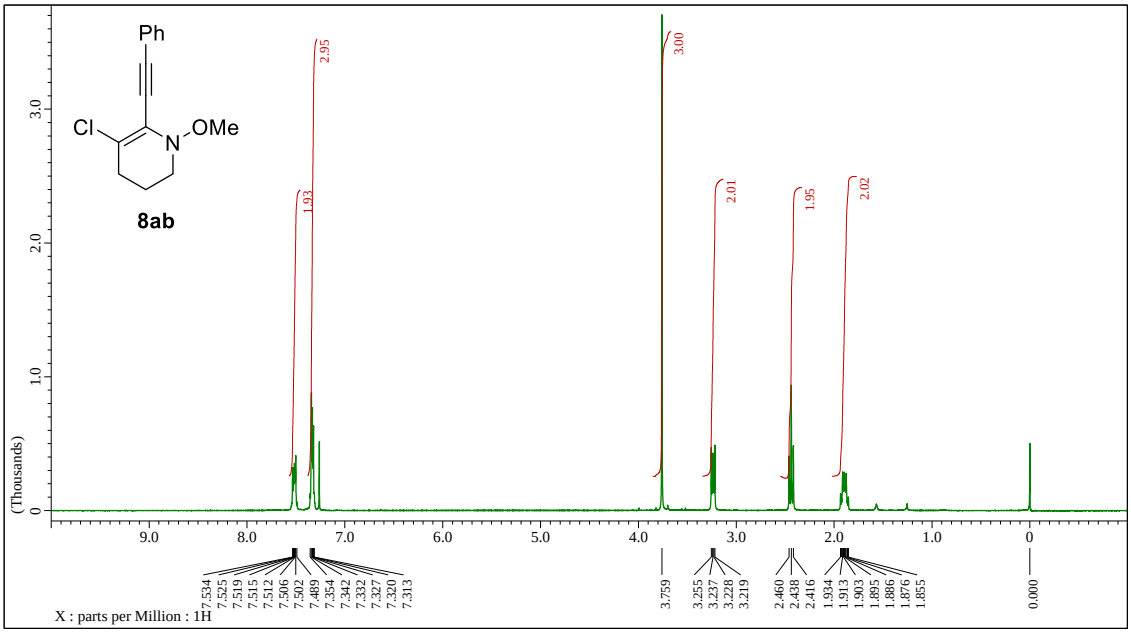
^{1}H-NMR (300 MHz, $CDCl_3$)



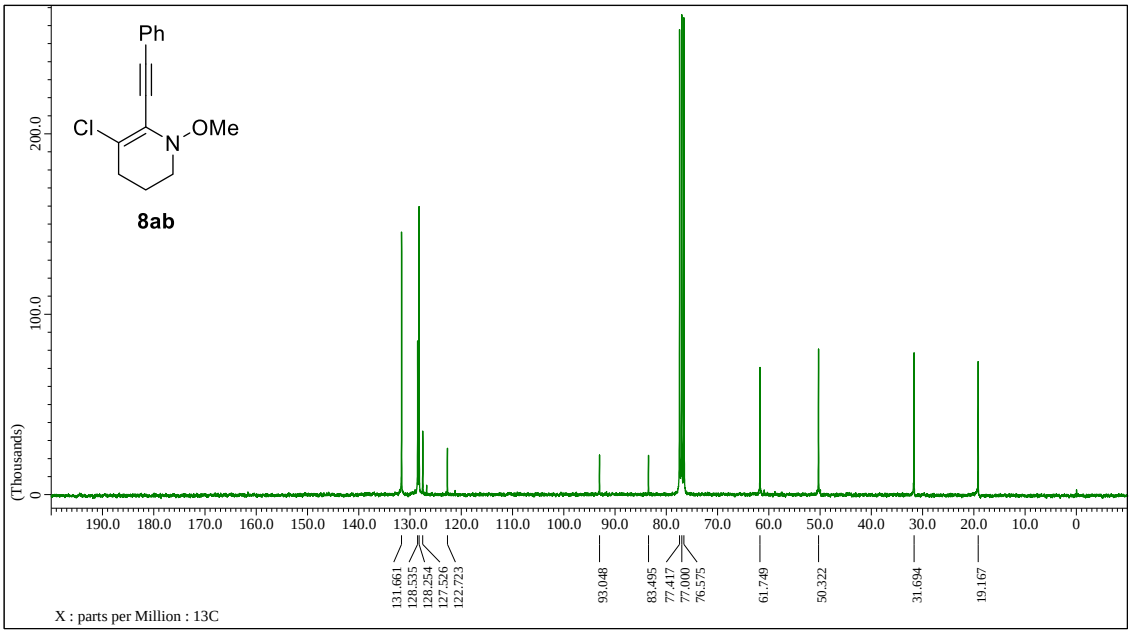
^{13}C-NMR (75 MHz, $CDCl_3$)



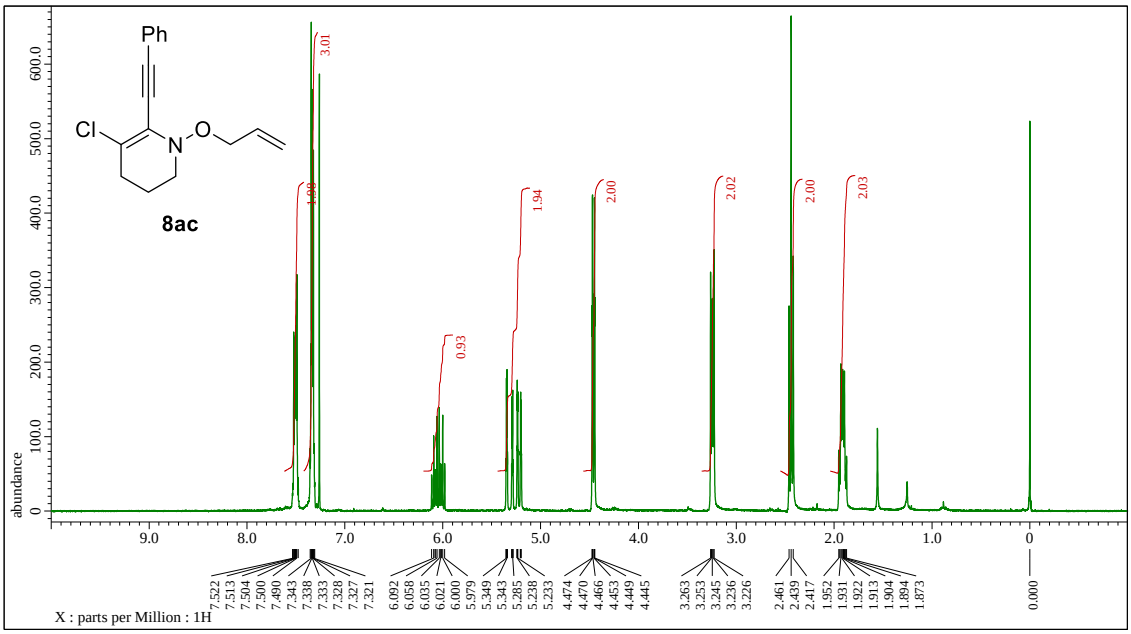
^{1}H-NMR (300 MHz, $CDCl_3$)



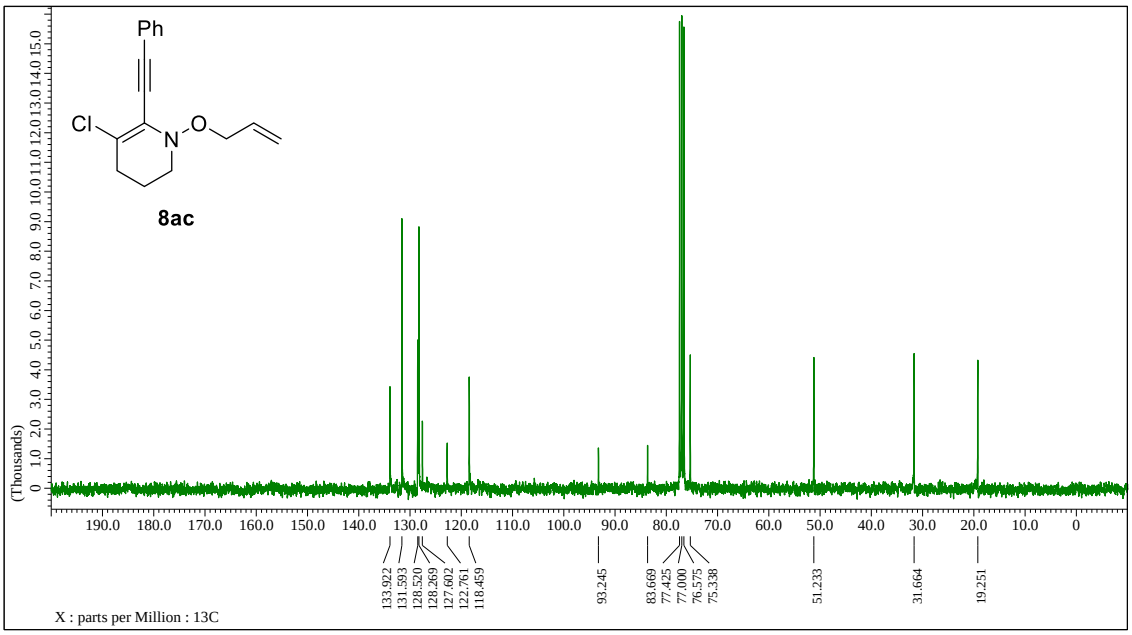
^{13}C-NMR (75 MHz, $CDCl_3$)



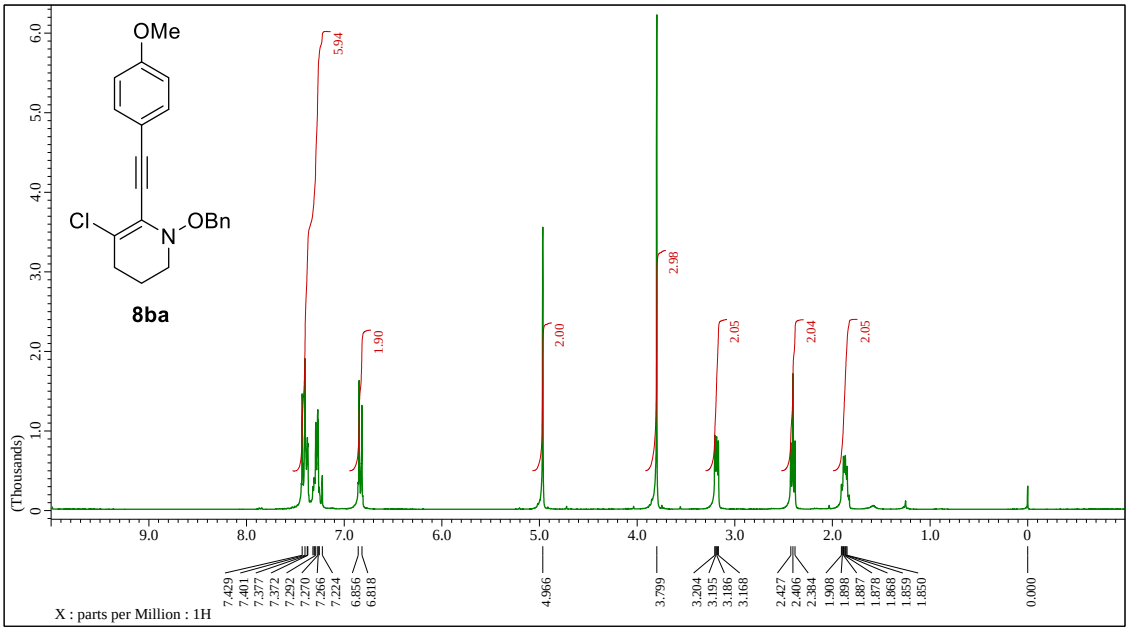
^{1}H-NMR (300 MHz, $CDCl_3$)



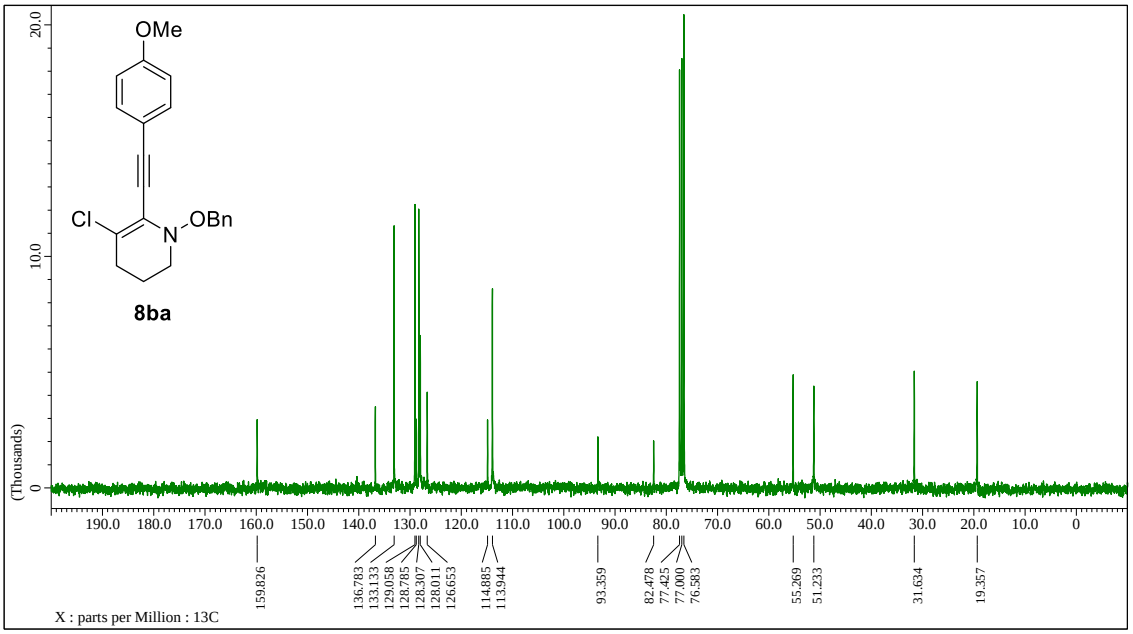
^{13}C-NMR (75 MHz, $CDCl_3$)



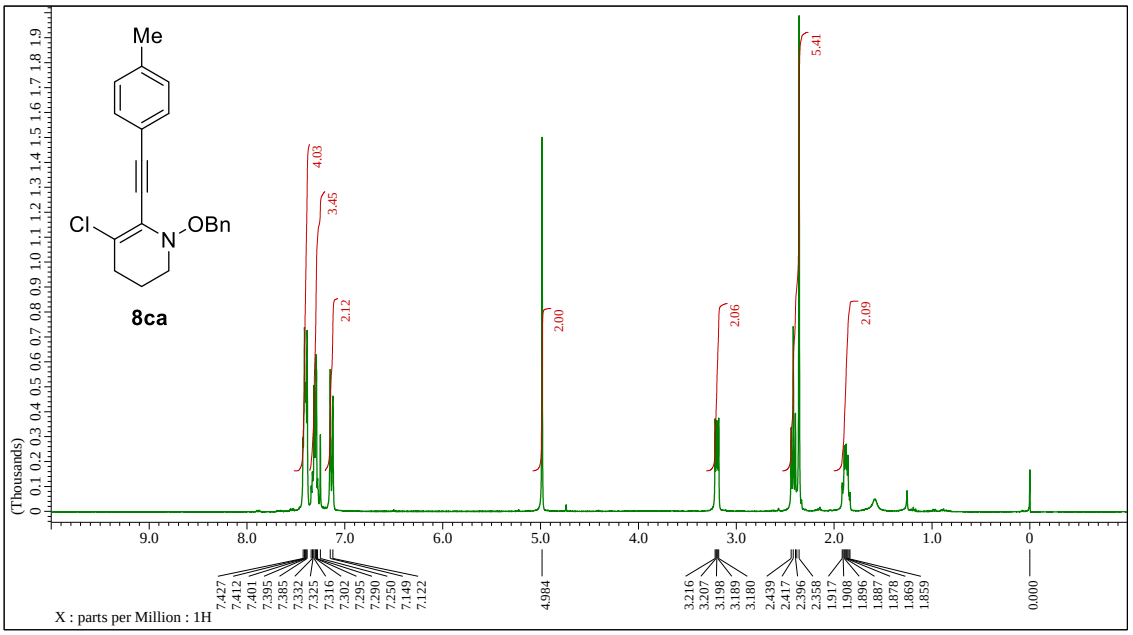
^{1}H-NMR (300 MHz, $CDCl_3$)



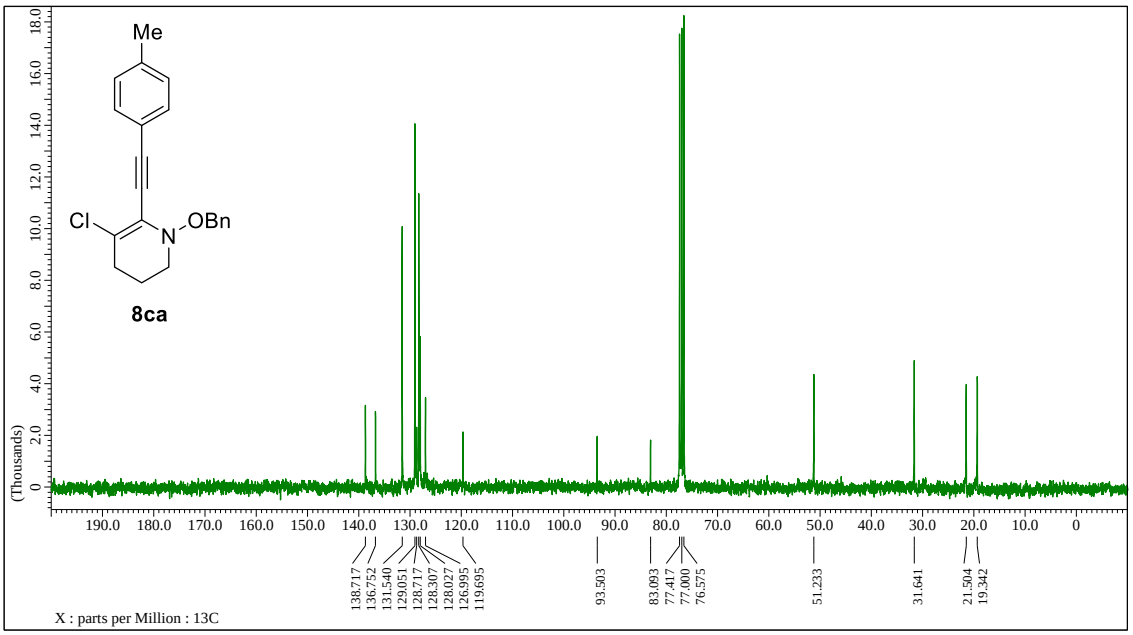
^{13}C-NMR (75 MHz, $CDCl_3$)



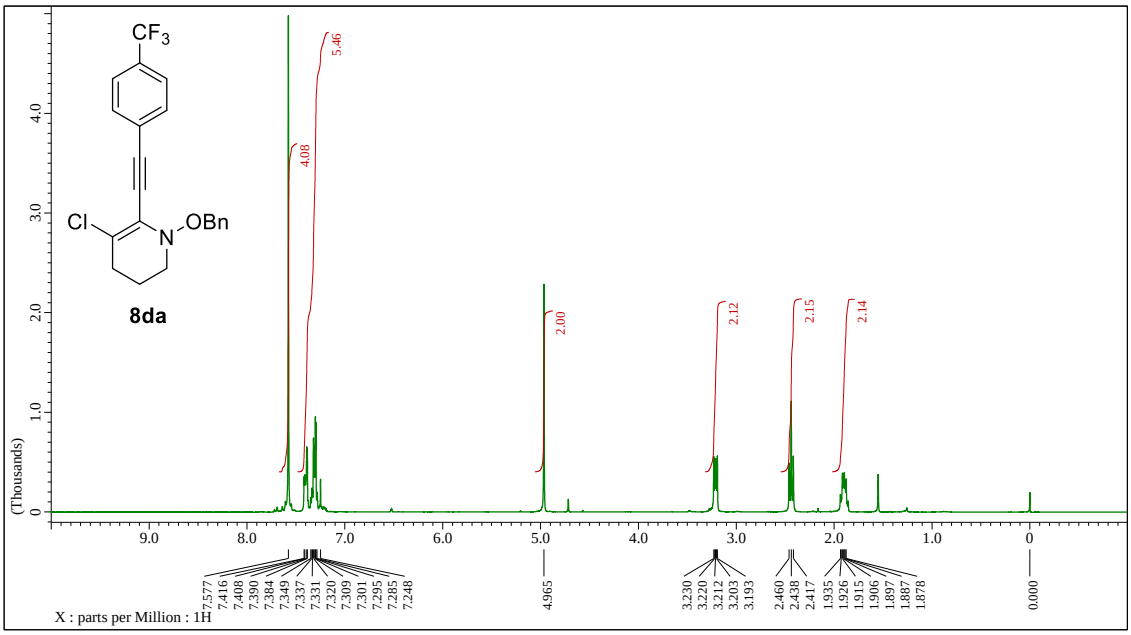
^{1}H-NMR (300 MHz, $CDCl_3$)



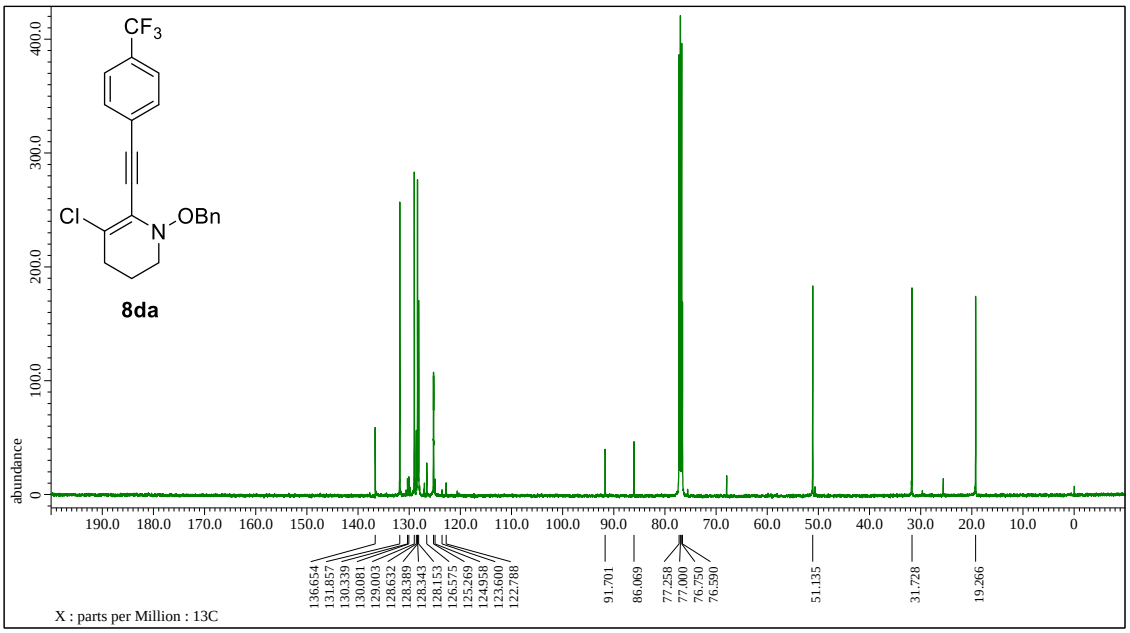
^{13}C-NMR (75 MHz, $CDCl_3$)



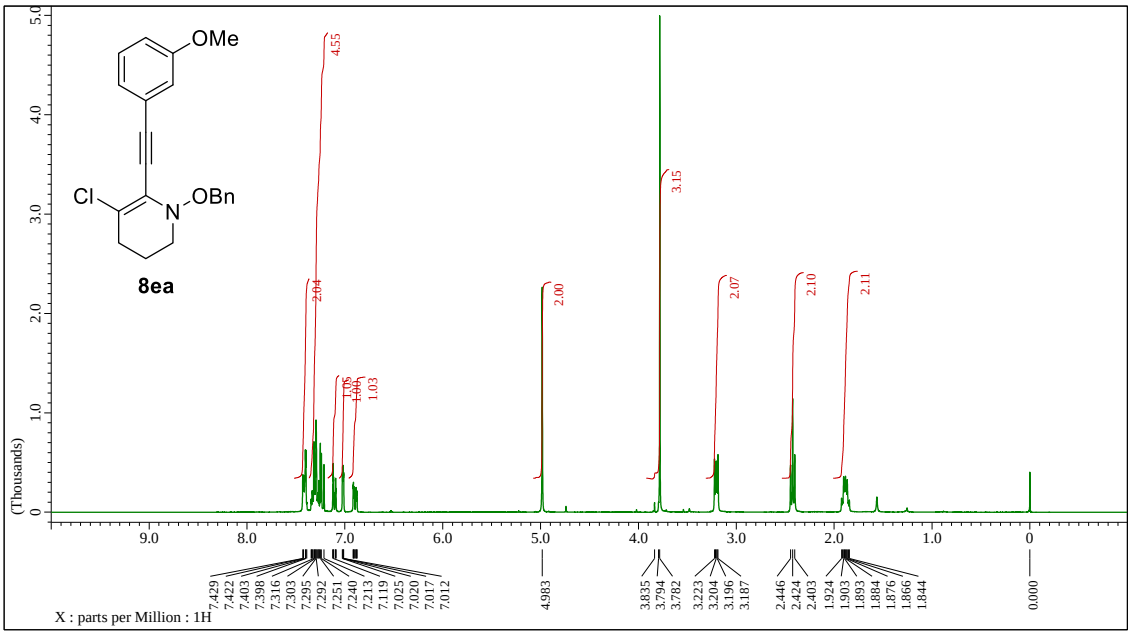
^{1}H-NMR (300 MHz, $CDCl_3$)



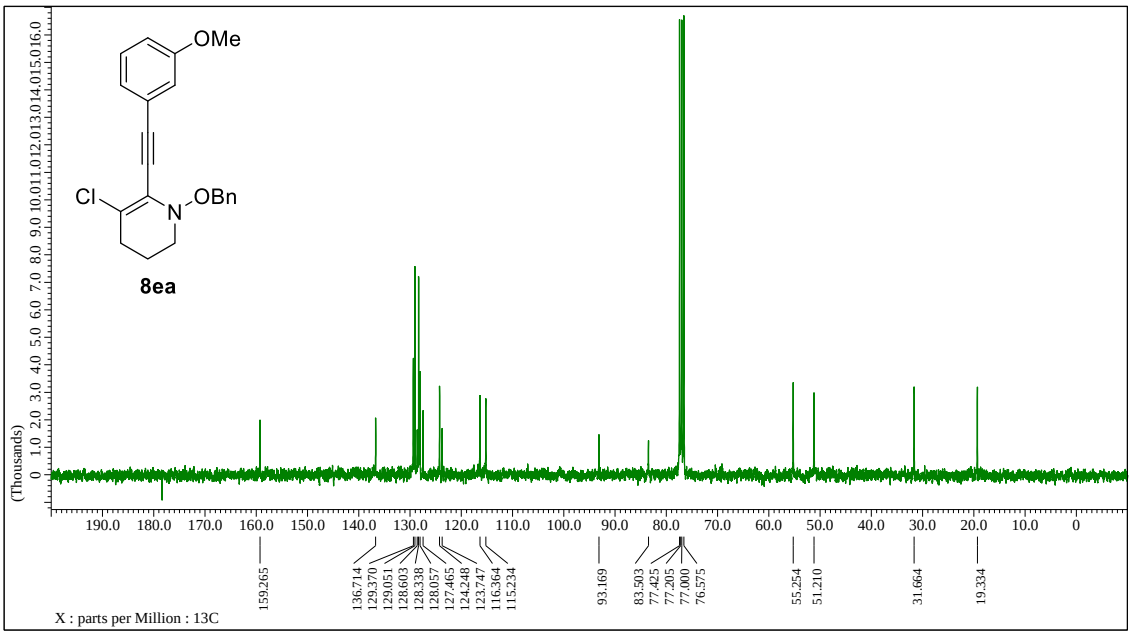
^{13}C-NMR (126 MHz, $CDCl_3$)



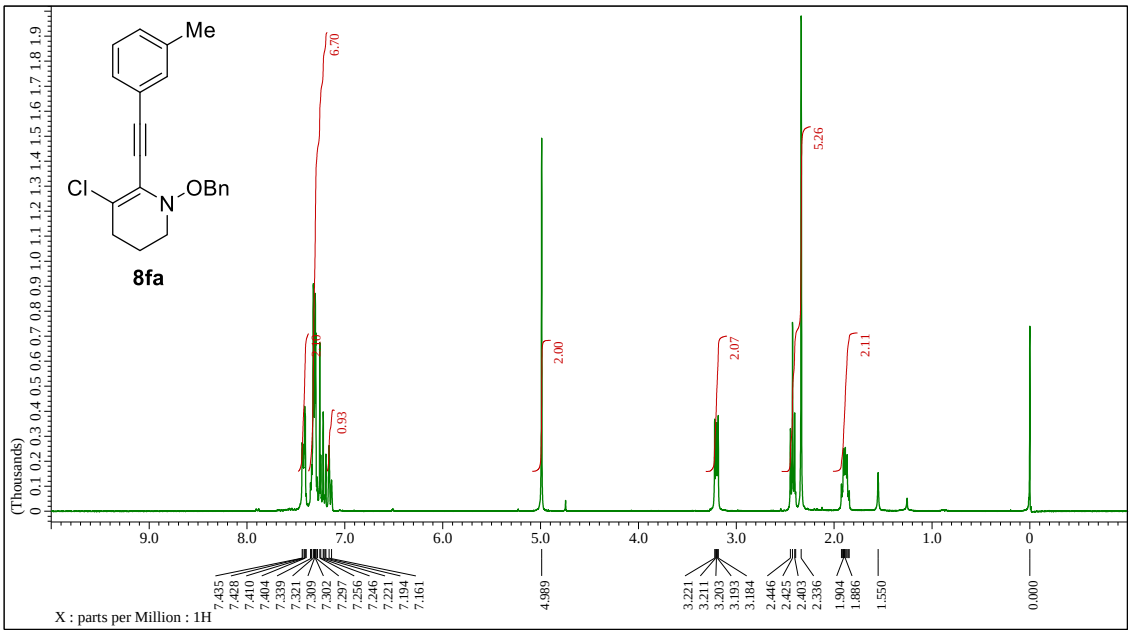
^{1}H-NMR (300 MHz, $CDCl_3$)



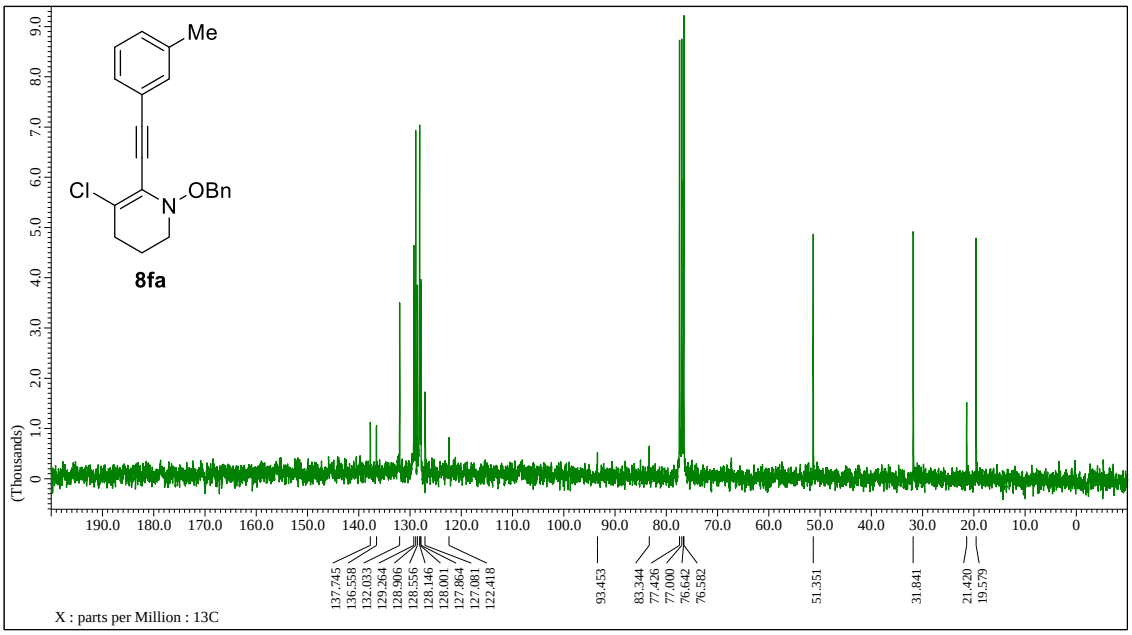
^{13}C-NMR (75 MHz, $CDCl_3$)



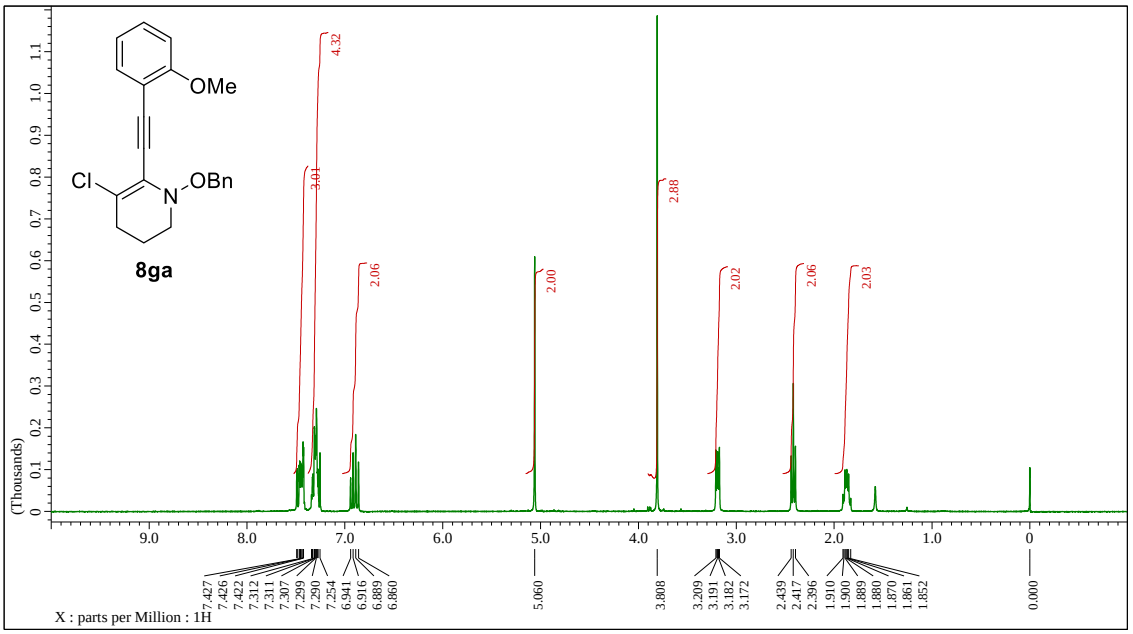
^{1}H-NMR (300 MHz, $CDCl_3$)



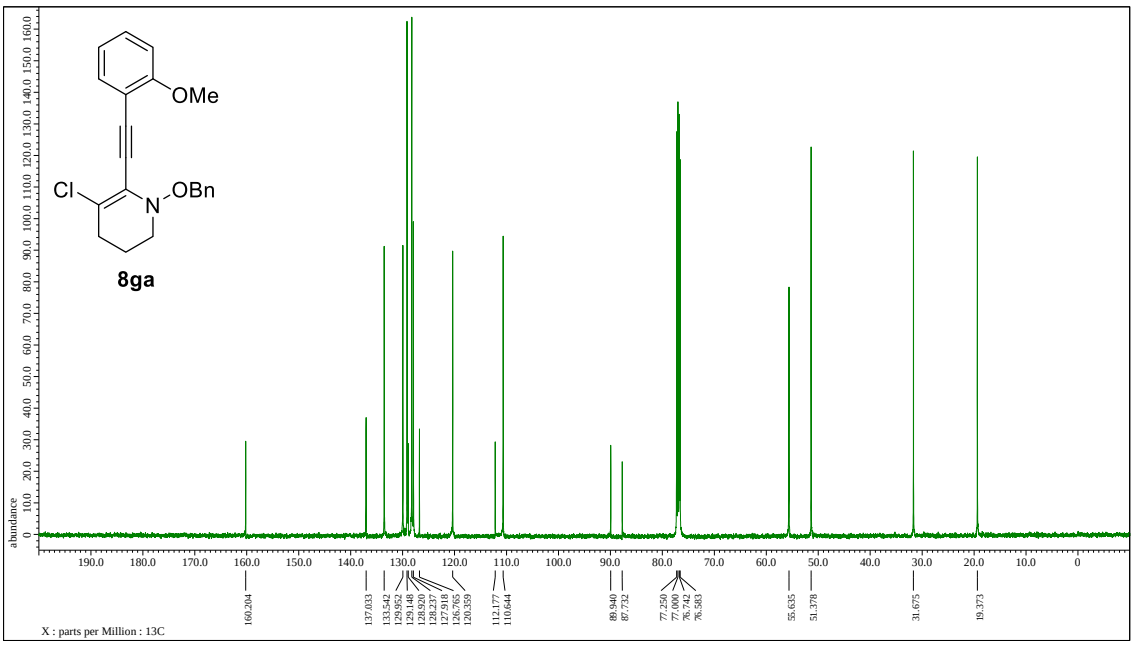
^{13}C-NMR (75 MHz, $CDCl_3$)



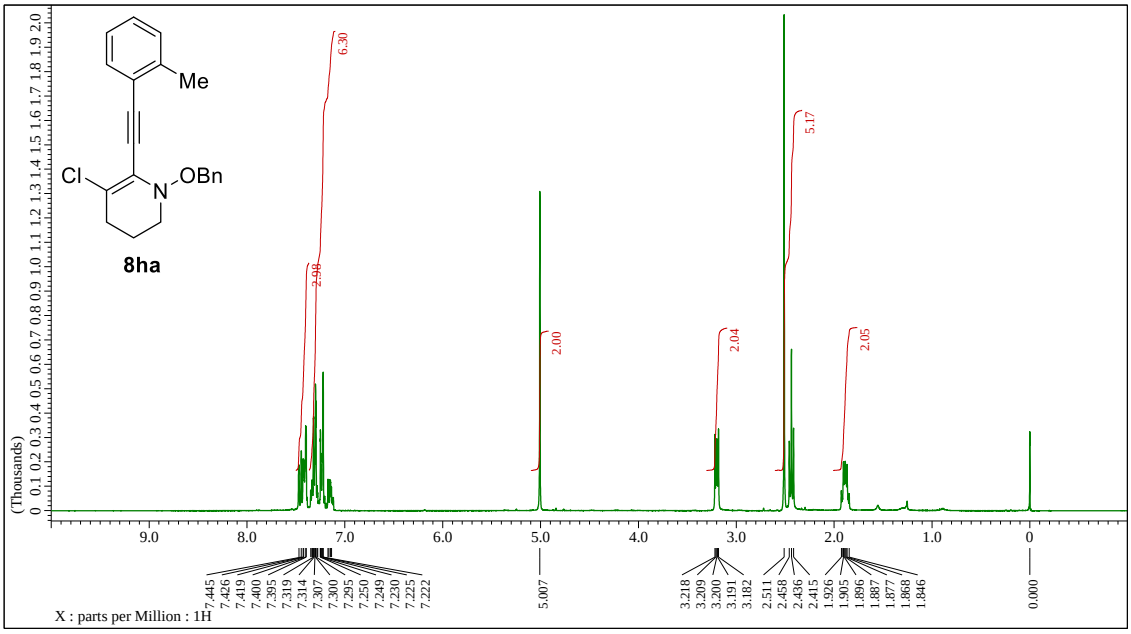
^{1}H-NMR (300 MHz, $CDCl_3$)



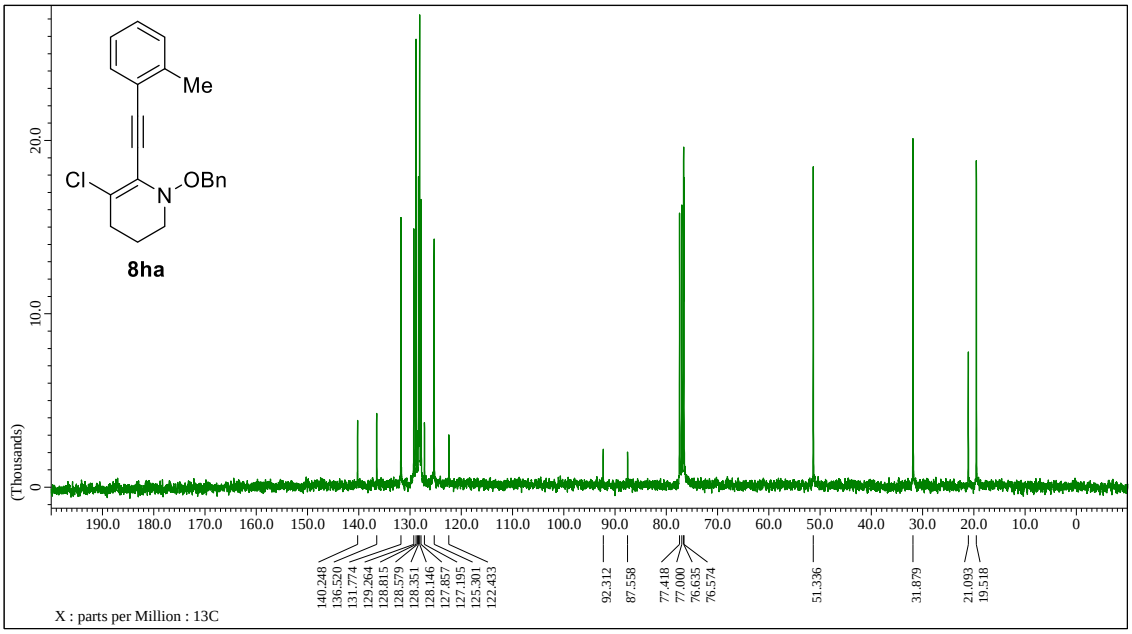
^{13}C-NMR (126 MHz, $CDCl_3$)



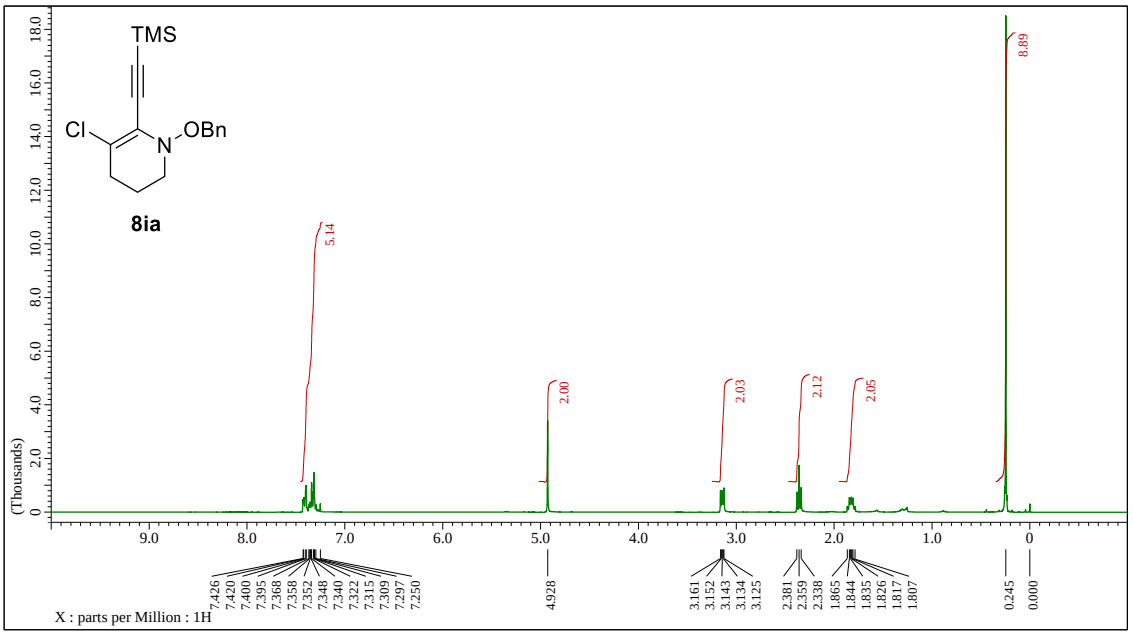
^{1}H-NMR (300 MHz, $CDCl_3$)



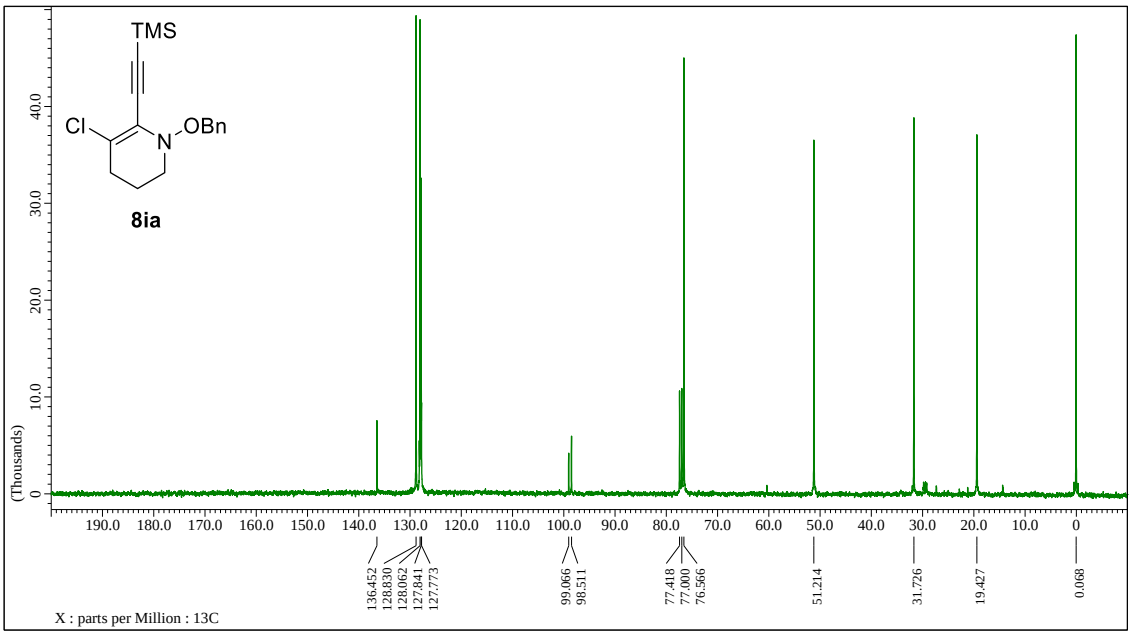
^{13}C-NMR (75 MHz, $CDCl_3$)



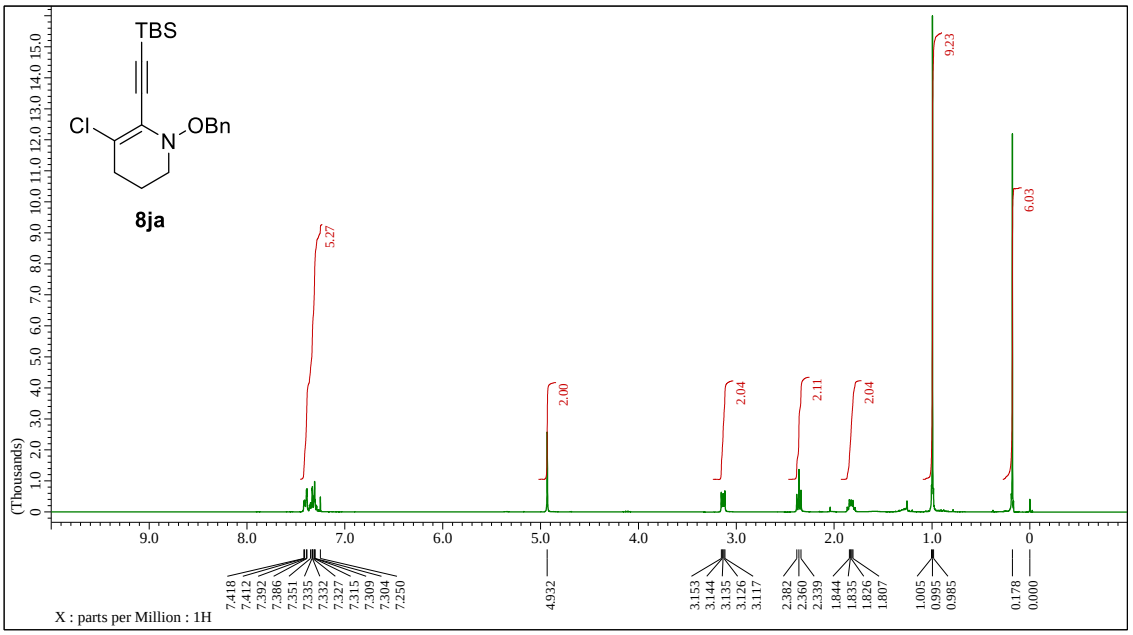
^{1}H-NMR (300 MHz, $CDCl_3$)



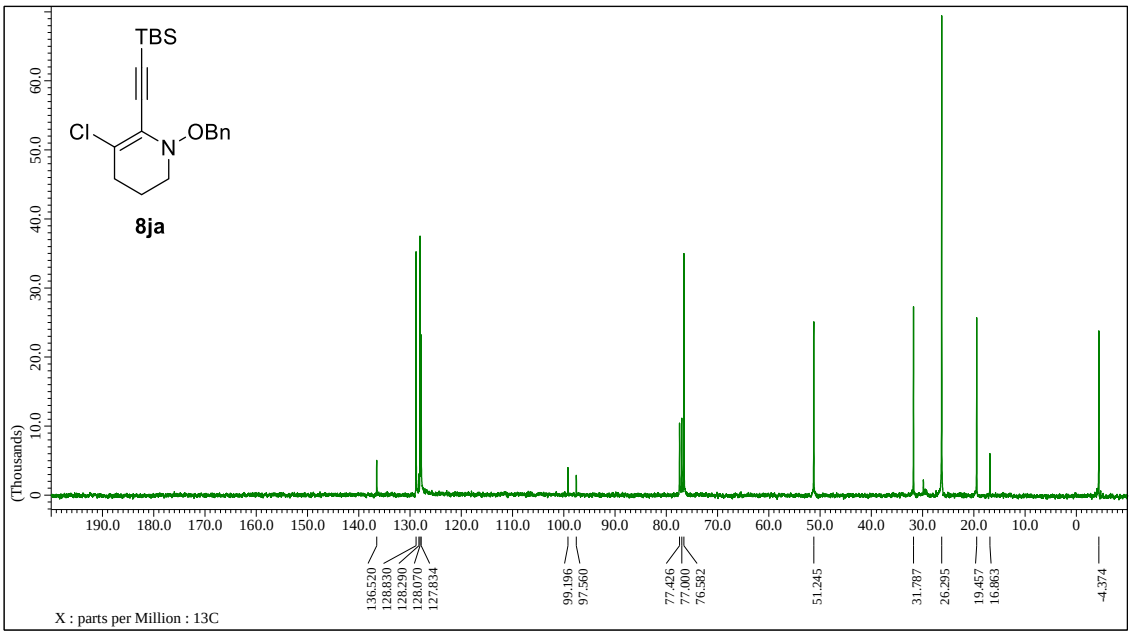
^{13}C-NMR (75 MHz, $CDCl_3$)



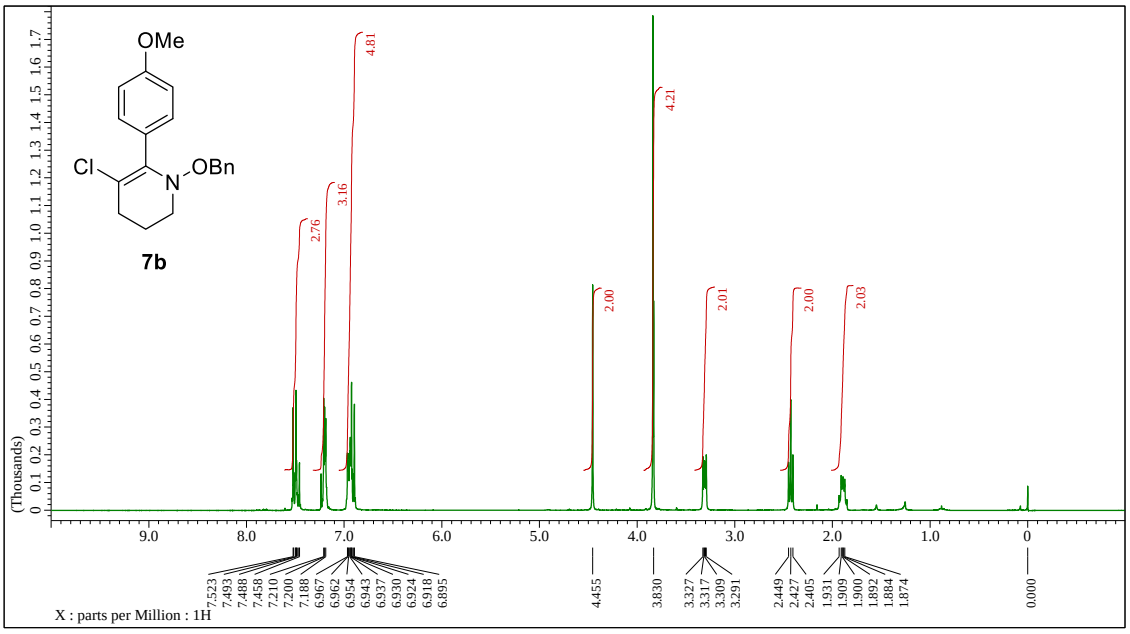
^{1}H-NMR (300 MHz, $CDCl_3$)



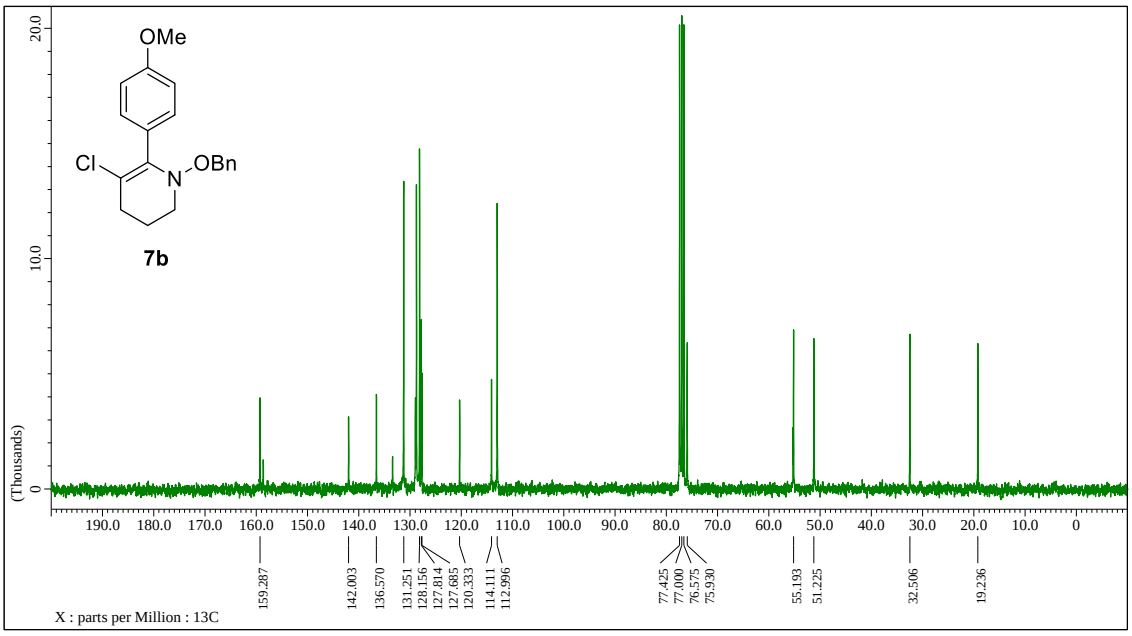
^{13}C-NMR (75 MHz, $CDCl_3$)



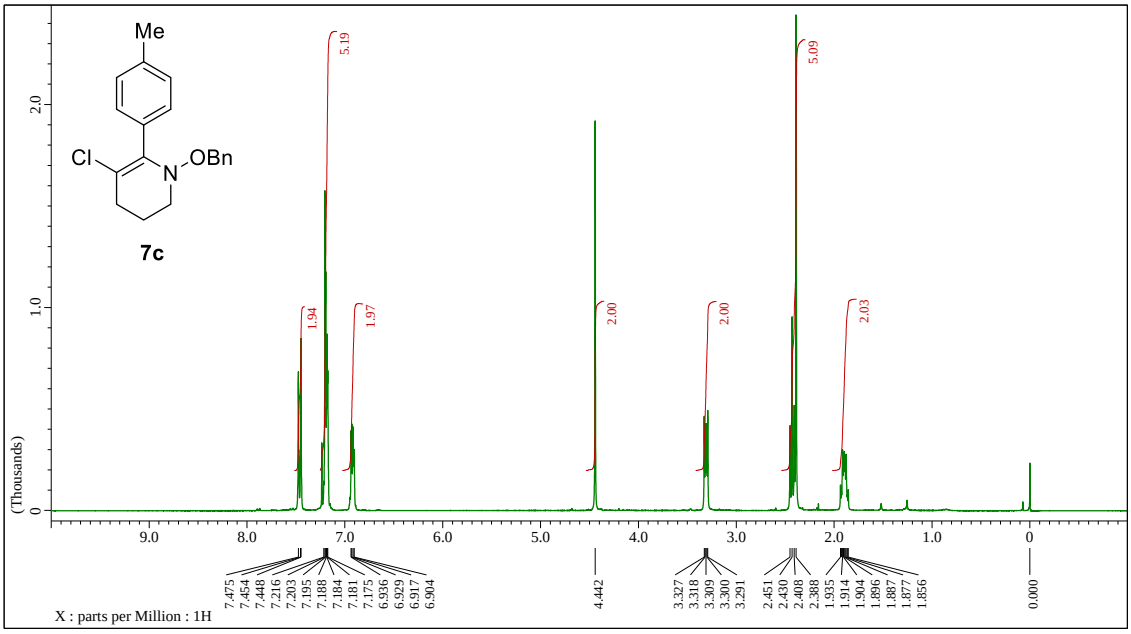
^{1}H-NMR (300 MHz, $CDCl_3$)



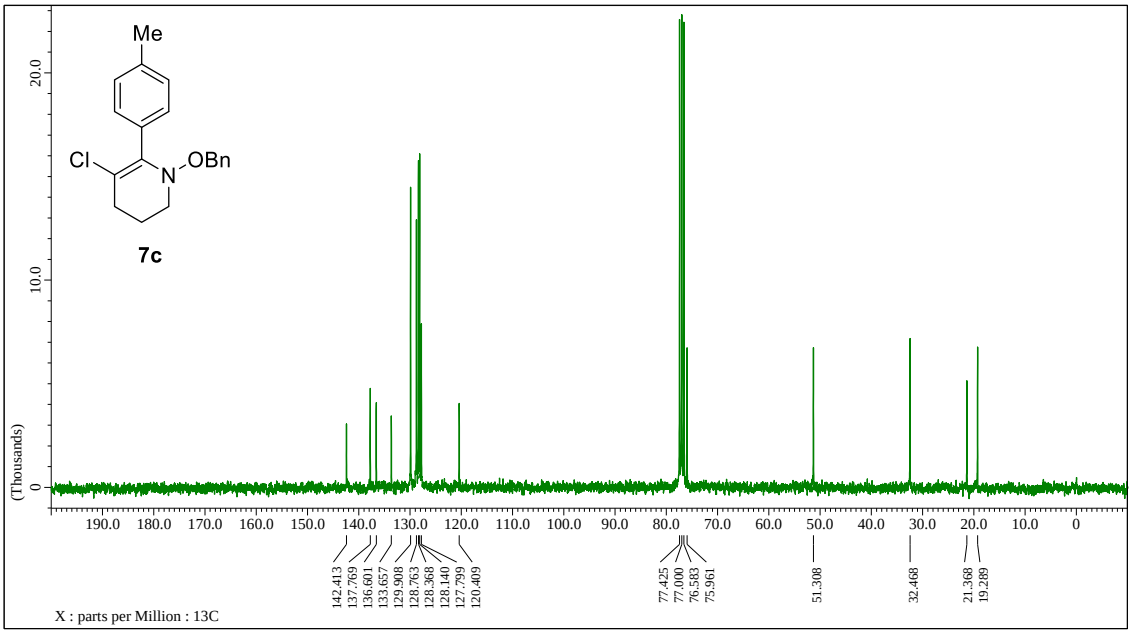
^{13}C-NMR (75 MHz, $CDCl_3$)



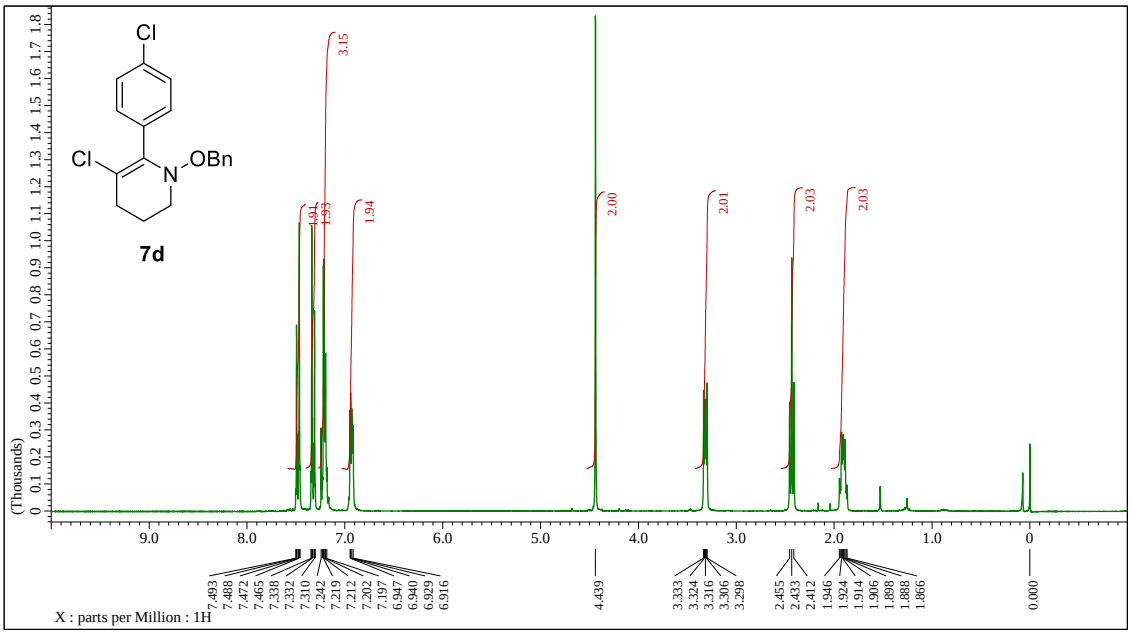
^{1}H-NMR (300 MHz, $CDCl_3$)



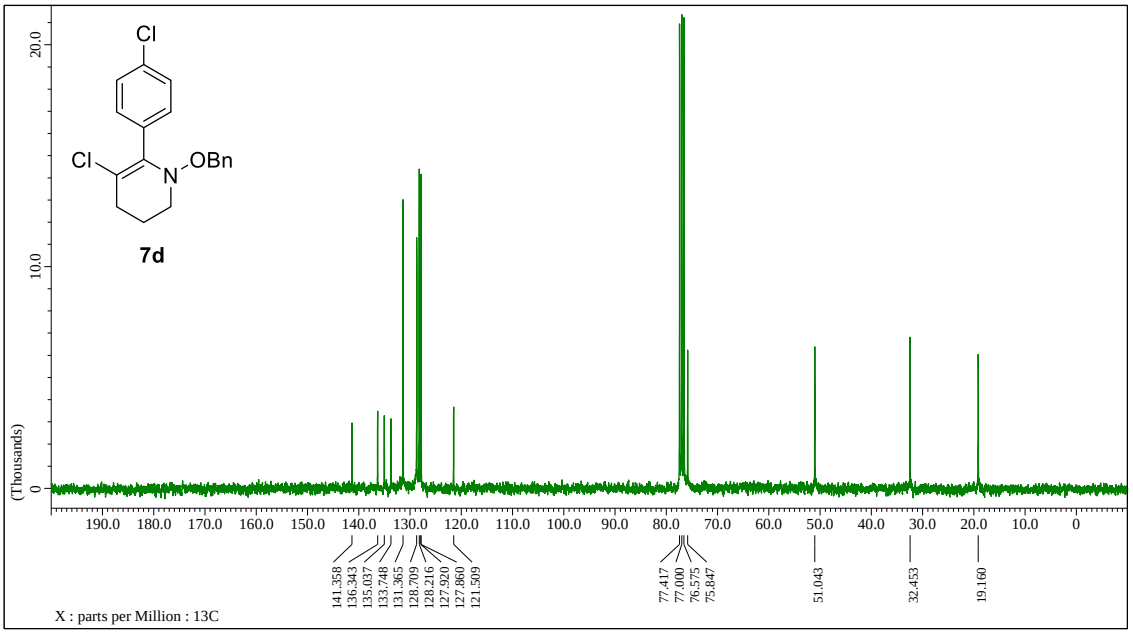
^{13}C-NMR (75 MHz, $CDCl_3$)



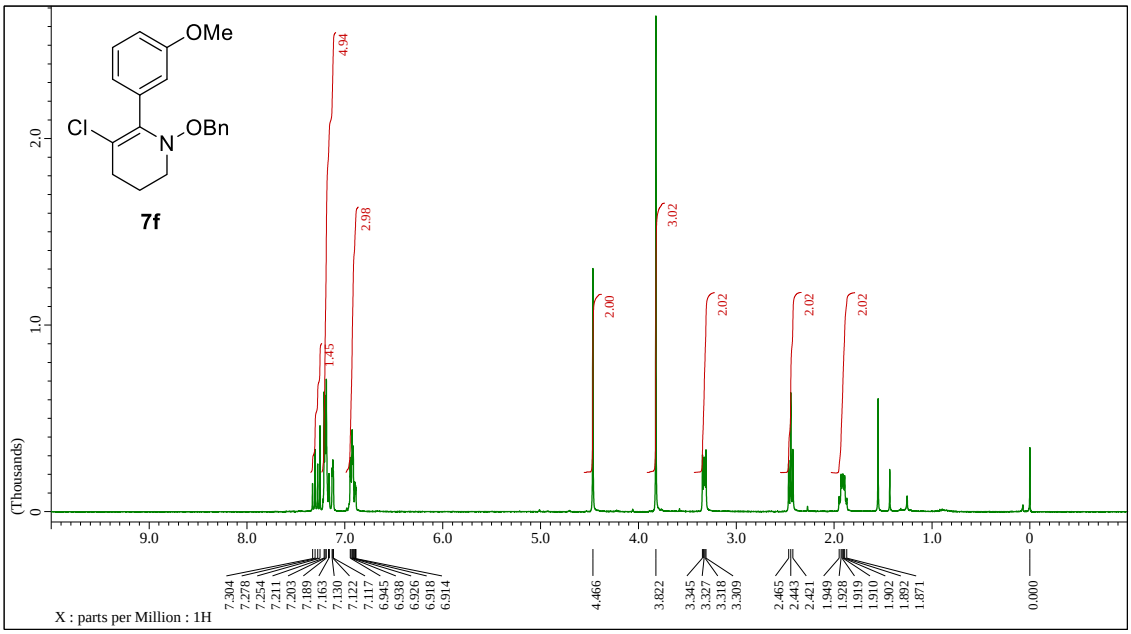
^{1}H-NMR (300 MHz, $CDCl_3$)



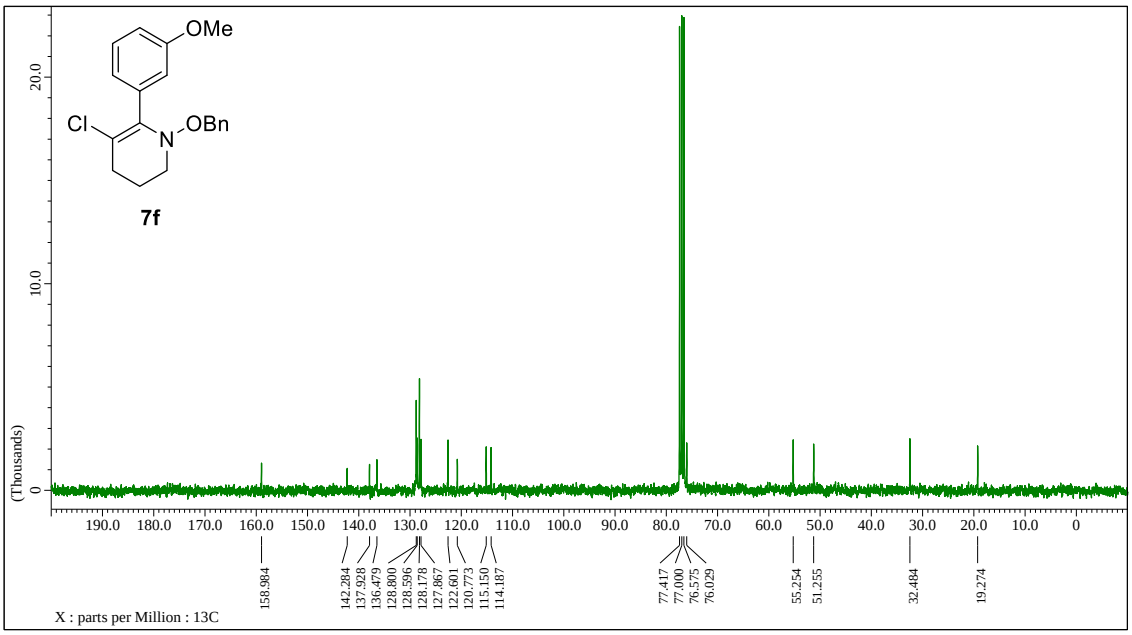
^{13}C-NMR (75 MHz, $CDCl_3$)



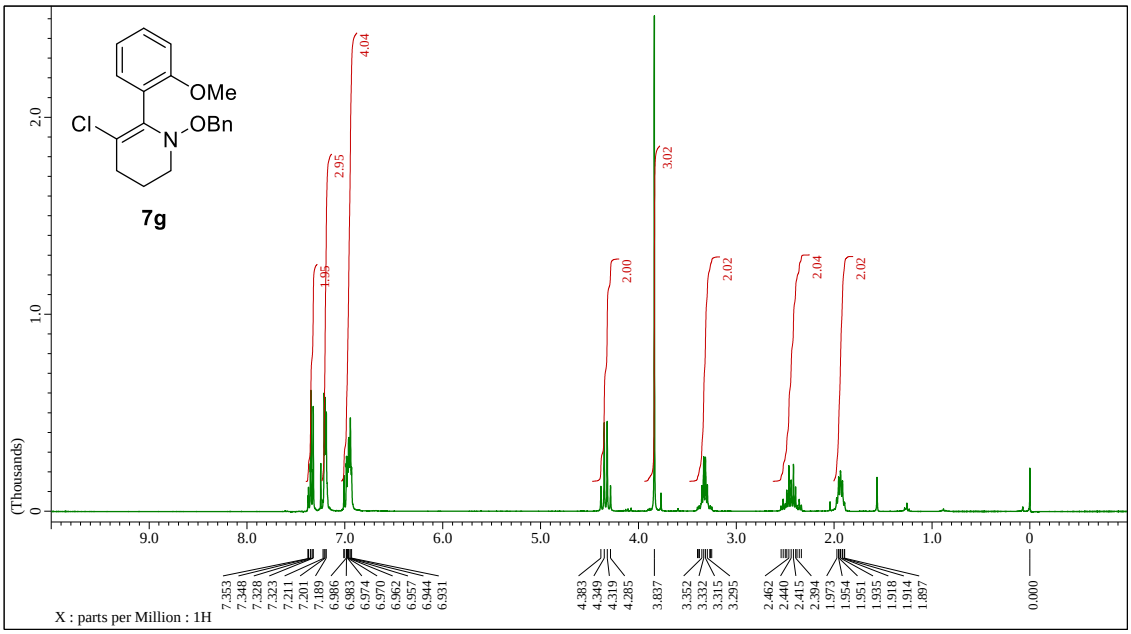
^{1}H-NMR (300 MHz, $CDCl_3$)



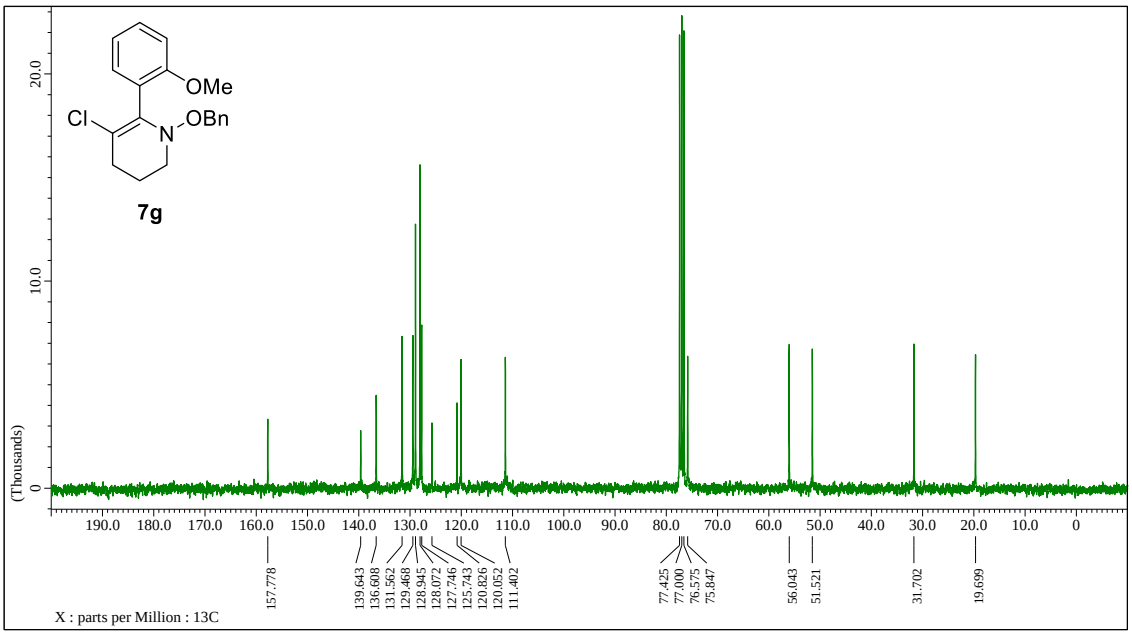
^{13}C-NMR (75 MHz, $CDCl_3$)



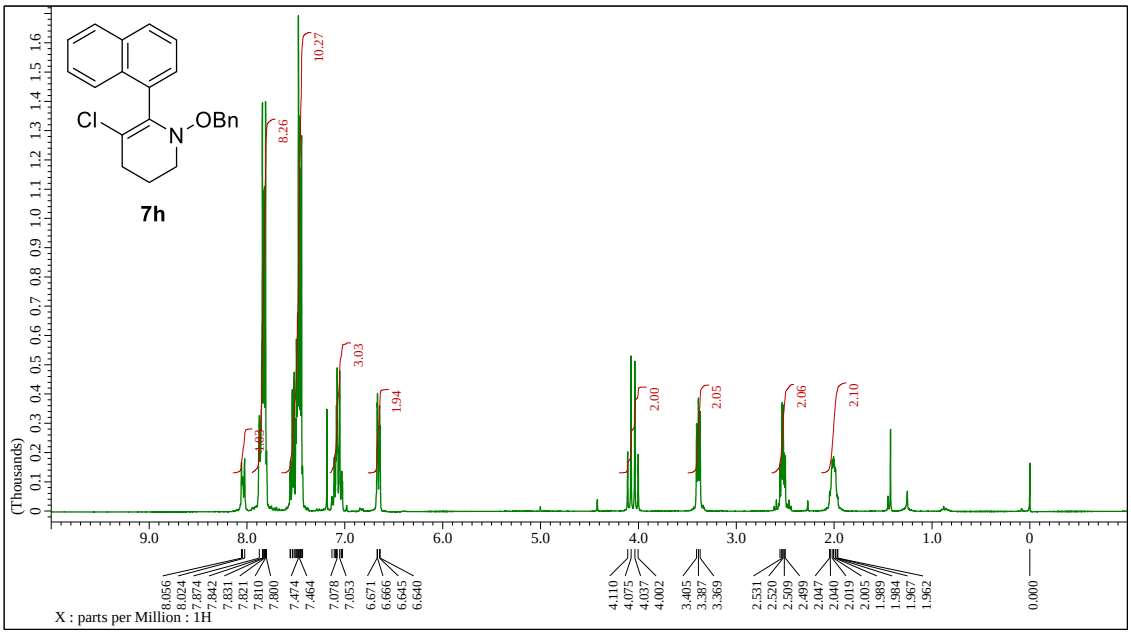
^{1}H-NMR (300 MHz, $CDCl_3$)



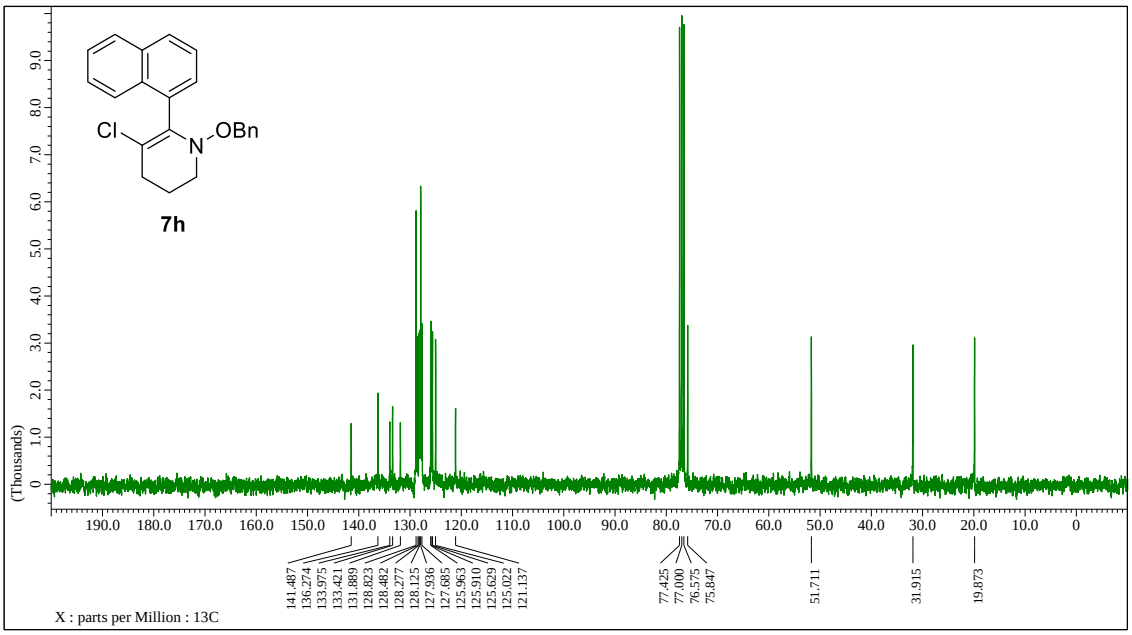
^{13}C-NMR (75 MHz, $CDCl_3$)



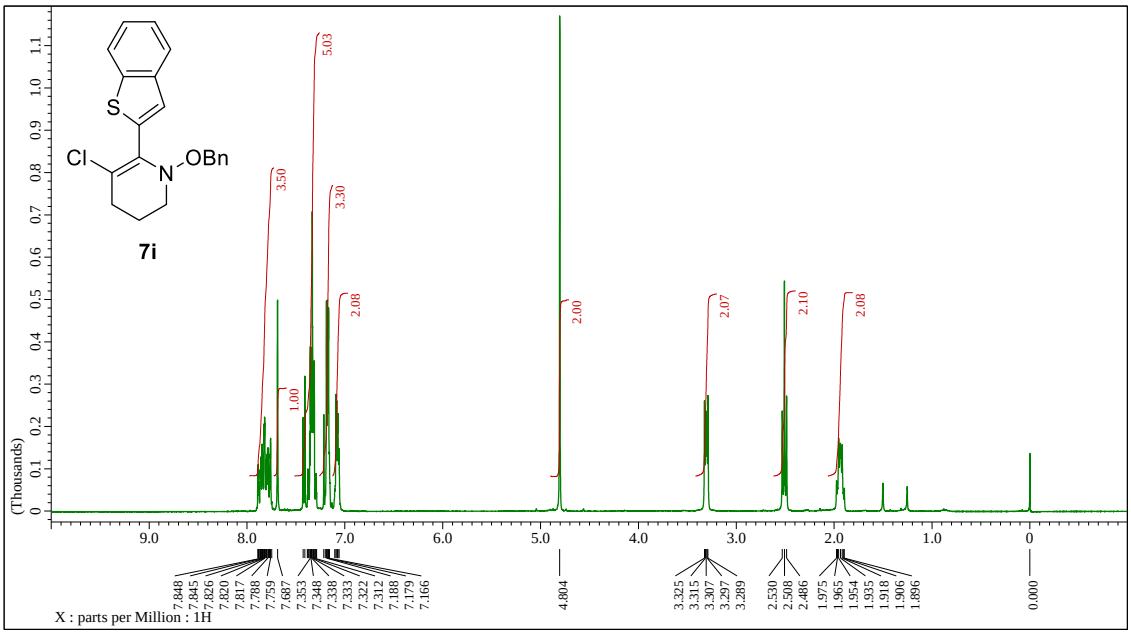
^{1}H-NMR (300 MHz, $CDCl_3$)



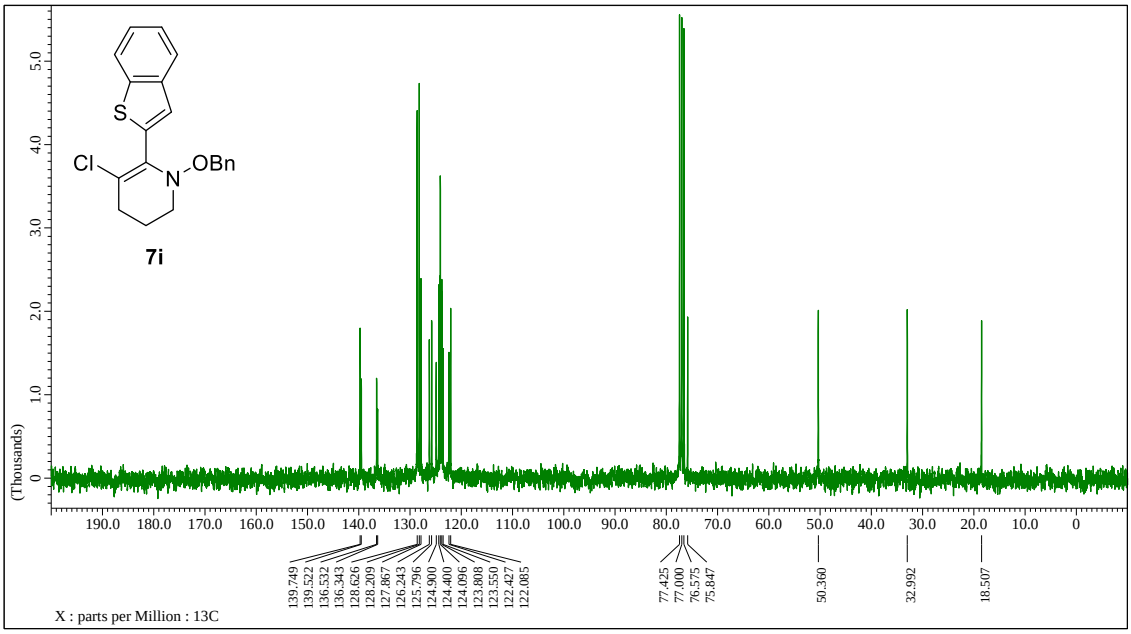
^{13}C-NMR (75 MHz, $CDCl_3$)



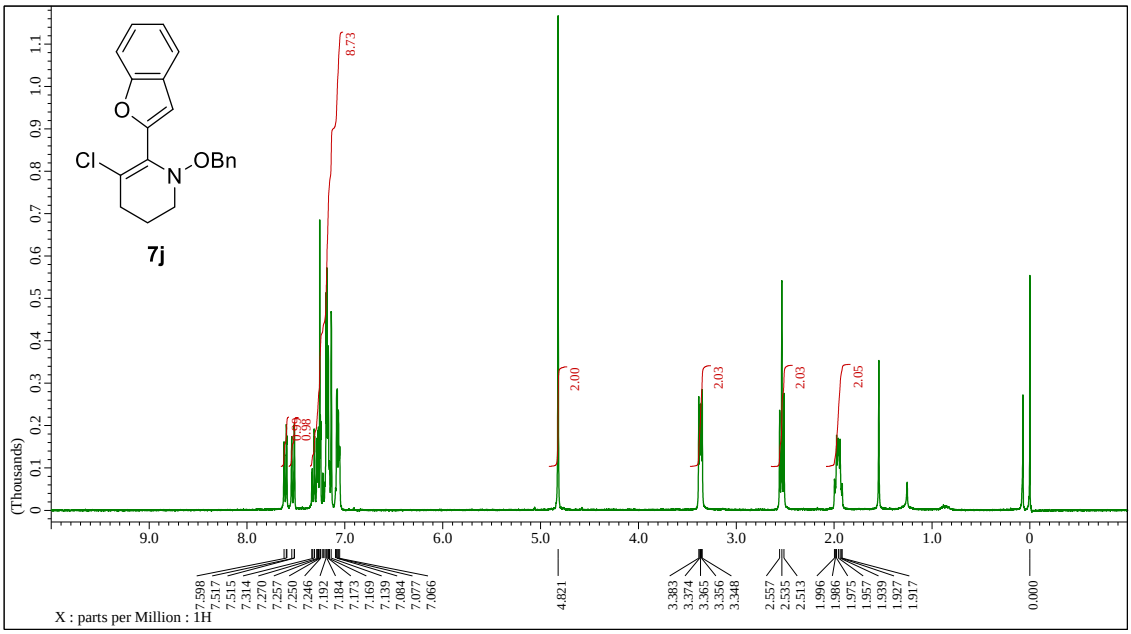
^{1}H-NMR (300 MHz, $CDCl_3$)



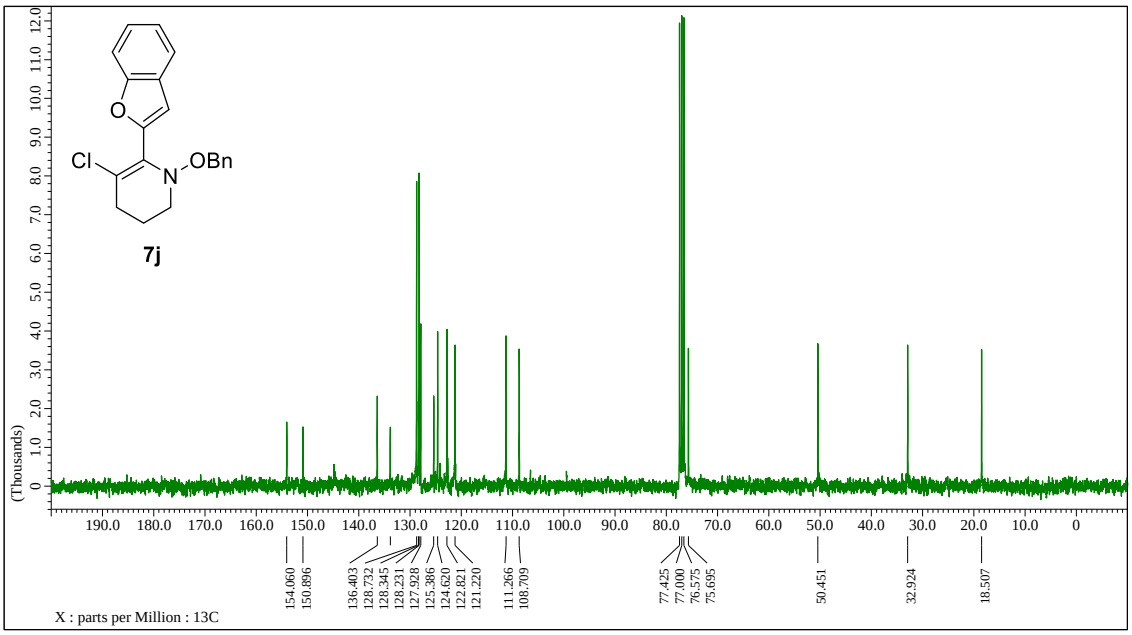
^{13}C-NMR (75 MHz, $CDCl_3$)



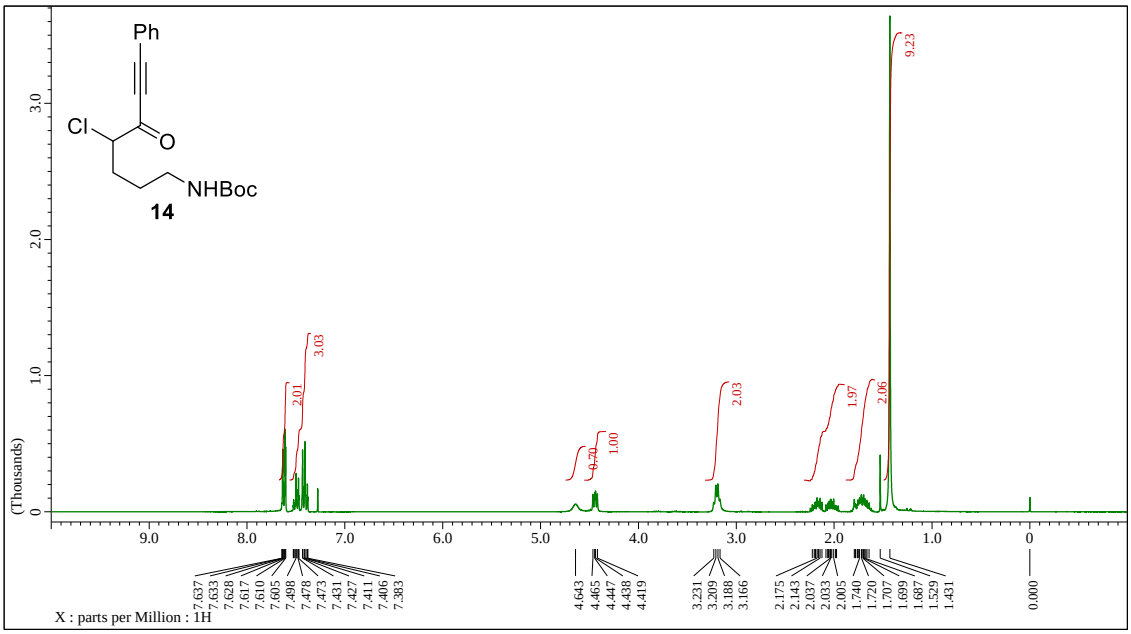
^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (75 MHz, $CDCl_3$)



^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (75 MHz, $CDCl_3$)